

SOME INVESTIGATIONS TO COMPARE THE DURABILITY AND  
PERFORMANCE OF MECHANICAL AND PORCINE HEART VALVE  
PROSTHESES

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### Formal Declaration

I declare that I have written the dissertation presented to the University of Edinburgh for the degree of Doctor of Medicine; that it is based upon my own observation and that, except as indicated in the thesis, the data were collected, analysed and interpreted by me.

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## ABSTRACT OF THESIS (Regulation 7.9)

The work reported in this thesis is an inherent part of research carried out in Edinburgh to assess the performance and durability of heart valve prostheses. From 1975 to 1979 540 patients undergoing heart valve replacement in Edinburgh Royal Infirmary were entered into a randomised trial and received either a mechanical (Bjork-Shiley), or porcine heterograft (Hancock or Carpentier-Edwards) prosthesis. Starting in 1977 in the United States the Veterans Administration carried out a similar randomised trial on 575 patients. After a mean period of 5 years no significant advantage to any of the three prostheses was observed, although there were some differences in the results reported in the Edinburgh and the US trials and possible explanations for these are proposed.

This thesis extends the analysis of the trial to a mean period of 10.5 years with respect to survival, and the incidence of reoperation, complications of anticoagulation, systemic embolism and bacterial endocarditis. It also presents a Doppler ultrasound comparison of the haemodynamic performance of the different valves in a subset of 102 patients.

After this extended follow-up period we have again observed no difference in survival between those receiving a mechanical or porcine prosthesis. Reoperation for valve failure was necessary significantly more often in patients with porcine prostheses (53 patients) than in those with the Bjork-Shiley prosthesis (17 patients). This difference was almost entirely due to cusp failure of porcine prostheses occurring more than 5 years after implantation. An actuarial analysis of valve survival using reoperation or cardiac death as end-points showed significantly better valve survival for patients receiving the Bjork-Shiley prosthesis when all patients and the subgroup undergoing mitral valve replacement were considered, but not in the subgroup receiving an aortic valve replacement.

All patients with Bjork-Shiley prostheses received longterm anticoagulation therapy, and bleeding complications were more frequent in this group. Death, reoperation, bleeding and complications of anticoagulation, systemic embolism and bacterial endocarditis were taken as end points for an actuarial analysis of "event-free survival". There was a non-significant trend in favour of the Bjork-Shiley prosthesis when all patients and the subgroup undergoing mitral valve replacement were considered, but no discernable trend after aortic valve replacement.

Doppler ultrasound techniques have been used to compare the haemodynamic performance of the Bjork-Shiley and porcine prostheses an average of 10 years after implantation in 102 patients enrolled in the Edinburgh trial. No significant difference in peak instantaneous or mean pressure gradient across the prosthesis was observed in patients who had undergone aortic or mitral valve replacement. There was however a significantly lower pressure half-time in patients with Bjork-Shiley compared with those with porcine mitral valve prostheses but this fell after exercise in those with porcine mitral prostheses, suggesting that this difference observed at rest does not indicate better haemodynamic performance of the Bjork-Shiley prosthesis.

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## CHAPTER 1

### INTRODUCTION

In 1923 Cutler and Levine reported successful treatment by closed mitral valvotomy of a 12 year old girl dying of severe mitral stenosis. The opening paragraphs of their report read:

"During the recent bicentennial of the former and present members of the nursing and professional staff of the Peter Bent Brigham Hospital, we presented a case of mitral stenosis upon which we had operated four days previously in an attempt to alleviate the condition by diminishing the degree of stenosis of the valve. It so happened that Professor Wenkebach of Vienna was visiting our clinic just at this time. The great enthusiasm and approval of the method of attack that he manifested, and the considerable discussion and general interest that the presentation of the case aroused, made it appear advisable to us to detail as exact a preliminary report as is possible at the present time."

Over the ensuing decades closed mitral valvotomy became established as a safe and highly effective treatment for patients with rheumatic mitral stenosis, and proved to be a successful treatment relieving symptoms usually for many years after operation. This procedure only requires conventional operating facilities and has brought the benefits of cardiac surgery to thousands of people not only in Western industrialised nations, but also throughout the Third World.

Patients with heavily diseased, fibrotic or calcified

mitral valves, those in whom fibrosis and calcification has progressed following initial successful valvotomy, and those with regurgitation of the diseased valve cannot benefit from valvotomy. In 1960, using techniques of cardiopulmonary bypass pioneered by Cooley (1958), Harken in Boston, Massachusetts and Starr in Portland, Oregon first used ball and cage mechanical prosthetic valves to replace diseased aortic and mitral valves in patients with severe heart failure (Harken et al 1960, Starr et al 1961). Only one of Harken's five patients survived to leave hospital. Starr's first patient died within 24 hours but six of the following seven survived. This operative treatment of patients with severe valvular heart disease radically changed the management of these patients and between 1963 and 1964 McGoon et al (1964) were able to report an unmatched surgical accomplishment at the Mayo clinic; the first one hundred patients in whom he replaced aortic valves survived. He almost exclusively used the prosthesis developed by Starr and Edwards, a device which is still used in modified form today and continues to be preferred by some surgeons. Operative mortality was also reduced dramatically following improvement in techniques of myocardial preservation, a major problem in valve replacement surgery being myocardial failure following cardiopulmonary bypass. This improvement was largely due to the introduction of cold potassium cardioplegia in addition to coronary perfusion (Richardson et al 1979).

Systemic embolisation was the most frequent complication of the Starr-Edwards and other mechanical

valve replacements, and early clinical experience with patients undergoing valve replacement with mechanical prostheses indicated that long term systemic anticoagulation with warfarin was essential if this risk was to be reduced (Barnhorst et al 1975). The persistent problem of thromboembolism and the need for anticoagulation with its attendant hazards led to the search for a suitable biological valve replacement; this would have a lower risk of thromboembolism, which might avoid the need for long term anticoagulant treatment. Ross (1962) and Barratt-Boyes (1964) used antibiotic sterilised homograft valves and achieved good medium term results (Barratt-Boyes 1977). Valves constructed from the patient's own fascia lata, at the time of valve replacement, proved to have only limited durability. In 1965 a glutaraldehyde-treated bioprosthesis from a calf was first used for valve replacement in a human (Binet et al 1965). Subsequently, heterograft bioprosthetic valves were produced commercially and were used widely. In some centres they became the type of prosthesis most frequently used for heart valve replacement, despite the absence of information about their long term durability. Carpentier, having taken part in the very early development of heterograft bioprosthesis, continued his work which led to the commercial development of the Carpentier-Edwards prosthesis. In 1976 when there was unbounded enthusiasm for the use of these bioprostheses, Carpentier himself stated: "We can predict that at the end of ten years the valve failure rate will be 20%" (Carpentier A, in discussion of Cohn L H et al 1976).

The first indications that bioprosthetic valves might prove to have limited durability were in children and young adults. In children prosthetic failure due to calcification of leaflet tissue frequently occurred within a few years of implantation necessitating reoperation (Curcio C A et al 1981; Magilligan D J et al 1985). Calcific stenosis of a bioprosthesis inserted in the mitral position has been reported in a young adult within a month of implantation (Forfar et al 1978).

Difficulties in the evaluation of the comparative merits of different types of prosthetic valve, whether mechanical or biological, are compounded by the effects of a variety of clinical features of patients undergoing valve replacement (Mitchell R S et al 1986). Age, sex, the presence of associated coronary artery disease, all influence outcome after valve replacement. Atrial fibrillation and enlargement of the left atrium are associated with systemic embolisation. Research carried out in the last 10-15 years has highlighted the influence of ventricular volume and function on survival and symptomatic status after valve replacement (Hammermeister et al 1978). The impact of all these "patient-related variables" complicates the evaluation of the effect of the type of prosthesis on patient survival, systemic embolisation and symptomatic status following valve replacement (Rahimtoola 1983).

The prospective, randomised controlled trial has long been established in the evaluation of different types of medical treatment, but has only infrequently been applied

in the evaluation of surgical procedures. Bioprosthetic valves had the advantage of an apparent reduced risk of thromboembolism, and by 1974 these valves had gained widespread acceptance and indeed were considered by many surgeons to be the optimal type of valve prosthesis for most patients. The durability of these devices had not however been established as it has been for mechanical prostheses and at that time no prospective randomised trial had been planned to compare the results of valve replacement using these prostheses with the already established mechanical prostheses. The time was right that the comparative merits of bioprosthetic and mechanical valves should be evaluated in the context of a prospective randomised controlled trial.

In 1975 Dr Hugh C Miller at Edinburgh Royal Infirmary, in collaboration with all the other consultant cardiologists in Edinburgh and with three cardiac surgeons, started a prospective randomised trial to compare early and long term results with the Bjork-Shiley tilting disc mechanical prosthesis, and with the Hancock porcine heterograft bioprosthesis. In 1977, in the United States, the Veterans Administration (VA) commenced a similar prospective randomised trial recruiting patients from thirteen different VA medical centres throughout the country in which the Bjork Shiley mechanical prosthesis was to be compared with the Hancock porcine bioprosthetic valve. Results of the Edinburgh trial, up to a median of 5.6 years of follow-up, were published in 1986 (Bloomfield et al 1986), and results of the VA cooperative study, also

up to a mean of 5 years of follow-up, were published in 1987 (Hammermeister et al 1987). These results are presented and compared in Chapter 2.

Patients enrolled in the Edinburgh trial have now been followed for a mean of 10.5 years (range 7.5 to 12.5 years) and the results are presented in Chapters 2 and 3. The aims of the study were:

- (1) To compare survival in the groups of patients receiving each type of prosthesis.
- (2) To compare the occurrence of complications possibly related to the type of prosthesis i.e. the need for reoperation due to valve failure, systemic embolisation, bacterial endocarditis, and bleeding related to the use of anticoagulant drugs.
- (3) To try to define which patients might benefit from the use of one type of prosthesis in preference to the other.

Until recently, there was no way in which the haemodynamic performance of the different prostheses could be compared after implantation without the use of invasive methods, that is cardiac catheterisation. This procedure is potentially dangerous in patients on anticoagulant treatment, and it was not carried out in patients enrolled in the Edinburgh trial. Cardiac catheterisation was carried out in about half of the patients enrolled in the VA Cooperative study shortly after surgery. Khuri et al reported in 1988 that, at six months after implantation, the Bjork Shiley valve appeared to possess marginally superior haemodynamic characteristics when used in the

aortic position, but there was no difference in the mitral position. No evidence was quoted from the VA Cooperative study on whether or not this superior haemodynamic performance equated with improved symptomatic results. Other workers have investigated the haemodynamic performance of implanted mechanical and bioprosthetic valves "in vivo", but this has almost invariably been with small numbers of patients and usually within one year of implantation (Bjork et al 1973, Lurie et al 1977, Cotter and Miller 1979, Thormann et al 1981, Horskotte et al 1983, Gray et al 1984).

With the accelerated degeneration of bioprosthetic valves which had been observed in children and young adults, it seemed likely that lesser degrees of degeneration and consequent impairment of haemodynamic performance might occur in adult patients implanted with such prostheses. Lipson et al (1982) studied a group of 54 patients undergoing valve replacement with the Hancock bioprosthetic porcine valve. All underwent catheterisation seven months after operation, and a further eighteen volunteered to have a second catheterisation seven years after operation. There was a significant increase in the mean pressure gradient across the mitral prosthesis over this period from  $5.9 \pm 0.7$  mmHg to  $8.6 \pm 0.7$  mmHg. The calculated valve area fell from  $2.2 \pm 0.2$  cm<sup>2</sup> to  $1.7 \pm 0.2$  cm<sup>2</sup>. Furthermore, in seven of the patients the valve area fell by more than 1 cm<sup>2</sup> over this period of time.

In patients implanted with mechanical prostheses in-growth of a panus of fibrin-like material has been observed



around the sewing ring on occasion causing dysfunction of the prosthesis (Yoganathan et al 1978). It appeared therefore that both types of prosthesis could be prone to deteriorate in performance over time (Roberts 1976). Furthermore, both mechanical and bioprosthetic valves are known to fail and to require replacement, the former most frequently because of thrombosis (Bjork and Henze 1979; Karp et al 1981) and the latter due to failure of the valve cusps. Bioprosthetic valve failure has been reported to be mostly gradual, but occasionally catastrophic. Thrombosis of the Bjork Shiley prosthesis usually leads to rapid clinical deterioration and often death unless thrombosis is reversed with thrombolytic treatment (Luluaga et al 1971), or the valve replaced.

Doppler ultrasound techniques enable measurement of the velocity of blood within blood vessels and the cardiac chambers. Light and Cross (1972) showed that the velocity integral recorded from blood flow in the aorta related to stroke volume. The development of Fast Fourier Transform spectral analysis of Doppler recordings of blood flow, facilitated the identification of the high velocities associated with valvular heart disease. Hatle and Angelsen used Doppler to measure these high jet velocities and predict valvular pressure gradients. The authors summarised their findings in the first clinical book exclusively written about Doppler methods in cardiology (Hatle and Angelsen 1982). Virtually all work published subsequently on the derivation of pressure gradients have been based on the concepts developed by them. These



concepts can also be applied to the measurement of pressure gradients across prosthetic valves and to the detection of associated regurgitant flow. This technique, therefore, for the first time enabled the haemodynamic performance of prosthetic valves to be assessed "in vivo" without using cardiac catheterisation.

A Doppler ultrasound machine was obtained in the Royal Infirmary in 1985 with which the function of prosthetic valves could be assessed. The aim of the work described in the latter part of this thesis was to determine if there was any difference in haemodynamic performance as determined by Doppler echocardiography between the Bjork Shiley and porcine bioprostheses 8 to 12 years after implantation.

## CHAPTER 2

### REVIEW OF THE EDINBURGH AND VETERANS ADMINISTRATION RANDOMIZED TRIALS COMPARING PORCINE AND MECHANICAL PROSTHESES. RESULTS AT 5 YEARS

The prognosis of patients with valvular heart disease is influenced by many factors. The age, sex, race, smoking habits, social class etc may be important influencing longevity in patients with valvular heart disease as in any other group of subjects. In addition the presence of associated coronary artery disease is known to influence survival following valve replacement (Czer et al 1984) and other factors such as ventricular function, the degree of pulmonary hypertension, the presence of atrial fibrillation, and other features would be expected to influence, not only survival, but the risk of morbid events such as systemic embolisation (Hammermeister et al 1978). It was clear, therefore, that a study to compare results after valve replacement with a porcine or mechanical prosthesis in a randomised trial would require a large enough group of patients so that these features would be equally represented in two treatment groups.

The Edinburgh heart valve replacement started in December 1975 and patients were allocated to treatment with a Hancock porcine valve prosthesis or a Bjork Shiley mechanical tilting disc prosthesis. In September 1977 The Veterans Administration (VA) Cooperative Study on Valvular Heart Disease was started and it too was to compare the Hancock porcine and Bjork-Shiley mechanical prosthetic valves; it was designed in a similar way to the Edinburgh

trial. Accession to the Edinburgh study was completed in August 1979, and to the VA study in September 1982, and I am fortunate to have a unique personal view of both studies. From July 1980 through June 1983 I worked in the Veterans Administration Medical Centre in West Roxbury Massachusetts, one of the largest centres participating in the VA study, and dealt with some of the patient population participating in the study. In 1983 upon returning to Edinburgh I was asked by Dr Hugh Miller to help with data collection and analysis of results of the Edinburgh trial, and I have also seen many of the patients participating in this study. The patient population, eligibility criteria and designs of the two trials are presented in this chapter; there are important differences in the populations studied in each trial and these are discussed later in this chapter and in chapters 3 and 4. The results after a mean of 5 years of follow-up are summarised from previously published work for both studies (Bloomfield et al 1986, Hammermeister et al 1987). As the main thrust of this thesis is an assessment of the long term results of valve replacement, only this part of the data is presented, and operative mortality is not discussed. The results of the Edinburgh study after a mean follow-up period of 10.5 years are presented in Chapters 3 and 4.

## **THE EDINBURGH STUDY**

### **Patients and Methods**

All patients requiring valve replacement who had been examined in the two hospitals involved in the study were seen by six consultant cardiologists and were considered

for entry to the study. Patients were excluded if long term anticoagulation was contraindicated, and those in the study who required another valve replacement were not reentered into the study. Three of the five cardiac surgeons participated in the trial.

A comprehensive clinical profile with 34 preoperative clinical variables and data from cardiac catheterisation was recorded for each patient (84.5% of the patients had cardiac catheterisation) Table 2.1. Coronary angiography was performed only when coronary artery disease was clinically suspected and disease was considered significant if there was a 70% or greater obstruction in a major coronary vessel.

At the time of the operation, if there were no technical reasons for preferring one prosthesis over the other, an envelope that indicated the prosthesis to be allocated to the patient was opened. Randomization of the envelopes was in groups of ten to ensure even distribution of prostheses should the trial need to be terminated prematurely or modified - as did in fact occur. The surgeons used a standardized technique, and cold cardioplegia was used routinely. Details of the size of the prosthesis, the total cross-clamp time, the total bypass time, the amount of blood transfused, and the need for postoperative inotropic support were all recorded.

Patients with Bjork-Shiley valves received warfarin indefinitely following surgery. All patients with porcine valves were given warfarin for two months post-operatively, but thereafter anticoagulation was at the discretion of the

TABLE 2.1

Data available for patients' clinical profile

Age

Sex

Valvular lesion

Aetiology of valve disease

NYHA clinical grade

Drug therapy, including anticoagulants

Previous thrombo-embolism

Previous cardiac surgery

12 lead ECG

Chest x-ray

\*Cardiac catheterisation data; right and left sided pressures, valve gradients, arterial and mixed venous oxygen saturation and cardiac index

Coronary angiography; vessels involved and severity of lesion

\*84 patients (15.5%) did not undergo cardiac catheterisation

referring physician and practice varied widely. Some physicians changed their patients' treatment during the course of the study and resumed anticoagulation that had previously been stopped. Any patient not on anticoagulants who developed an embolus was automatically restarted on anticoagulants.

## **Methods**

The majority of patients were followed up by one of the principal investigators or by their local physician. Thirty-six patients were interviewed by questionnaire. Details of any possible embolic event were specifically sought, and any residual signs were documented. Valve failure was defined to include malfunction of the prosthesis, endocarditis, or multiple embolic events that resulted in the death of the patient or replacement of the prosthesis. After successful reoperation, patients were withdrawn from the study.

Deaths related to the valve replacement operation were defined as those that occurred before hospital discharge. Other deaths were classified as cardiac, noncardiac, or possibly cardiac, on the basis of the clinical and autopsy evidence available. In addition, deaths were classified as prosthesis-related if this was appropriate. Deaths due to embolism or a complication of anticoagulation were classified as cardiac, and deaths due to embolism or occurring at reoperation were classified as prosthesis-related.

Statistical analysis employed the t-test for the continuous variables of age and follow-up length, and the

Fisher exact test and the Pearson Chi-square test for categorical analysis. The rates of survival, valve failure, thromboembolism, and anticoagulant-related haemorrhage were expressed in the form of standard life tables. The generalized Wilcoxon and Mantel-Haenzel tests were used to test for differences in survival. Continuous data are presented as mean  $\pm$  SD, and actuarial probability estimates as mean  $\pm$  2 SEM.

Of the 811 patients who underwent valve replacement in Edinburgh Royal Infirmary during the study period, 612 were referred for valve replacement to the three participating surgeons. Seventy-two of these patients were excluded from the study because of inability to take anticoagulants or because there were technical reasons to prefer one type of prosthesis, and the 540 remaining patients were randomized. Because of their low number, the eight patients who underwent tricuspid valve replacement were excluded from further analysis. Of the remaining patients, 262 had mitral valve replacement, 210 had aortic valve replacement, and 60 had combined aortic and mitral valve replacement.

From December 1975 to January 1977, patients randomized to treatment with a porcine xenograft prosthesis received a Hancock prosthesis (107 patients), but thereafter because of cost, the Carpentier-Edwards prosthesis was used (159 patients). Patients randomized to receive a mechanical prosthesis received the Bjork-Shiley valve throughout (266 patients). It seemed possible that time of operation might exert a separate bias, but results of valve replacement with Bjork-Shiley prostheses were

similar in the two time periods, consequently results were analysed as a simple comparison of the three prostheses.

The randomization procedure worked well, and there was no statistically significant difference in the distribution of any of 34 preoperative variables among groups identified by prosthesis used for patients having aortic, mitral, or aortic plus mitral valve replacement. Patients not catheterised preoperatively were randomly distributed in the three treatment groups, and the three surgeons were also equally represented.

## **RESULTS**

### **Late Postoperative Deaths**

Of the 487 patients leaving hospital, only six were lost to follow-up. The median duration of follow-up was 5.6 years (range 2.8 - 8.3 years). There were 113 late deaths during this follow-up period. The causes of death (cardiac, possibly cardiac, non-cardiac, or not known) are categorised in Table 2.2. Where death could be attributed to the prosthesis this is also shown in Table 2.2. In several cases death was sudden and information from an autopsy was not usually available.

### **Reoperation for Valve Failure**

Details of the 37 patients who underwent a reoperation for replacement of the randomised prosthesis are listed in Table 2.3. There was no significant difference in the need for valve re-replacement in patients in the three prostheses groups. Thrombotic obstruction was the commonest reason for reoperation for those receiving the Bjork-Shiley prosthesis, and degeneration of the cusps of



TABLE 2.2

## EDINBURGH HEART VALVE STUDY. RESULTS AT FIVE YEARS

## CASES OF LATE POSTOPERATIVE DEATHS

	Bjork-Shiley (n = 266)	Hancock (n = 107)	Carpentier- Edwards (n = 159)
<u>Cardiac Death</u>			
<u>Prosthesis Related</u>			
Embolism	2	1	
Complication of			
Anticoagulation	2		
Thrombosed Valve	3		
Valve dysfunction	3	1	3
Endocarditis	2	1	1
Reoperation	4	4	3
Total	16	7	7
<u>No Prosthesis Related</u>	17	4	3
Autopsy Performed	11	2	4
Total	37	15	10
<u>Possible Cardiac Death</u>	9	4	9
Autopsy performed			
<u>Non Cardiac Death</u>	14	6	4
Autopsy Performed			
<u>Not Known</u>	2	1	2
Total	62	26	25

TABLE 2.3

## EDINBURGH HEART VALVE STUDY. RESULTS AT FIVE YEARS

## REOPERATION FOR VALVE FAILURE

Prosthesis	AVR	MVR	AVR + MVR	Total	Died	<u>Valve failure</u>		SBE
						Intrinsic failure	Peri- prosthetic Leak	
Bjork-Shiley (n = 266)	5	7	3	15	4	8	6	1
Hancock (n = 107)	*4	5	3	12	4	5	4	2
Carpentier (n = 159)	+1	6	3	10	3	6	2	1
Total (n = 532)	10	18	9	37	11	19	12	4

\*19 mm AVR removed due to persisting gradient  
+Details of one MVR reoperation not available

SBE = Subacute Bacterial Endocarditis

those receiving the porcine prosthesis. The incidence of periprosthetic leaks was similar in the three treatment groups, and in all 12 patients with this complication the valve was intact at operation. Endocarditis precipitated a second operation in four patients (two with a Bjork-Shiley prosthesis, and one each with a Hancock and Carpentier-Edwards prosthesis).

### **Survival**

Actuarial survival curves for all patients in the study showed no significant differences among the three prostheses during seven years (mean, 5.6 years) of follow-up postoperatively (Figure 2.1). Actuarial survival for all patients was  $63.2 \pm 8.7\%$  at seven years. For patients undergoing aortic valve replacement, actuarial survival was  $69.6 \pm 9.6\%$  at seven years (Figure 2.2), for mitral valve replacement it was  $56.7 \pm 7\%$  (Figure 2.3) and for aortic plus mitral valve replacement it was  $62.5\% \pm 20.0\%$ . There was no significant difference in overall survival for the different prostheses in any of these treatment groups.

### **Thromboembolism**

Only the first embolic event was considered in actuarial analysis, though 12 patients had more than one embolus. Eight patients with a Bjork-Shiley prostheses (six with mitral, one with aortic, and one with aortic plus mitral valve replacement) had a total of 20 embolic events. Two patients with Carpentier-Edwards prostheses had four emboli. Actuarial analysis of survival and survival free of embolism was performed for aortic valve and mitral valve replacement patients to compare the three types of

FIGURE 2.1

Edinburgh Heart Valve Study: Results at 5 Years

Actuarial survival curves, including in-hospital mortality (Hosp), for all patients undergoing mitral, aortic and mitral plus aortic valve replacement. The numbers below the figure indicate the patients at risk during follow-up.

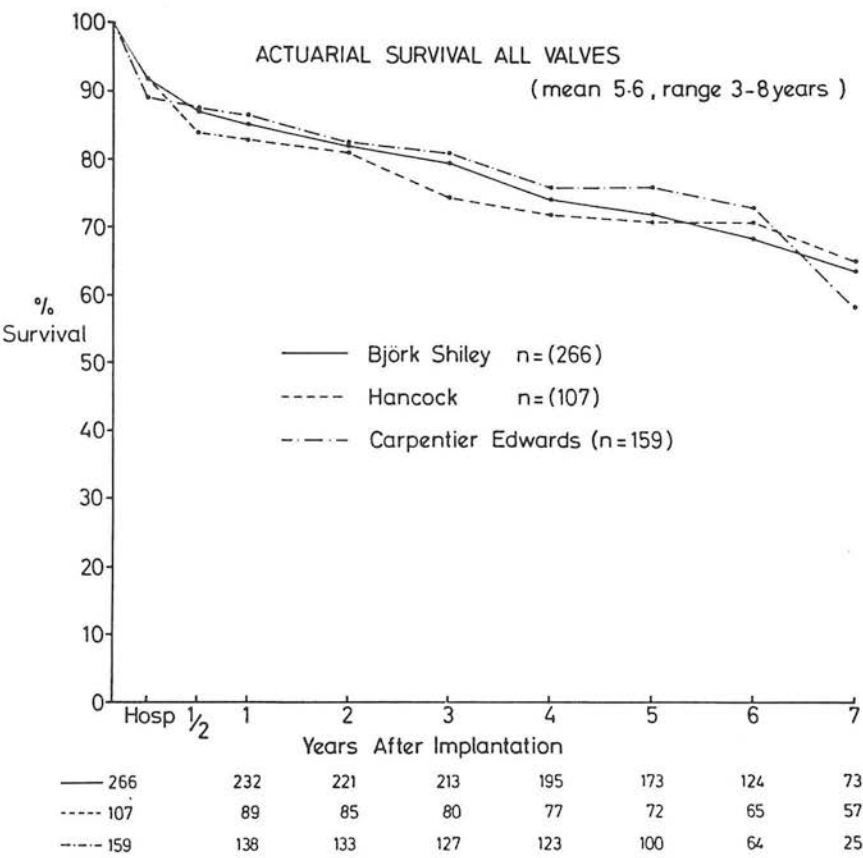


FIGURE 2.2

Edinburgh Heart Valve Study: Results at 5 Years

Actuarial survival curves for patients undergoing aortic valve replacement with each type of prosthesis used.

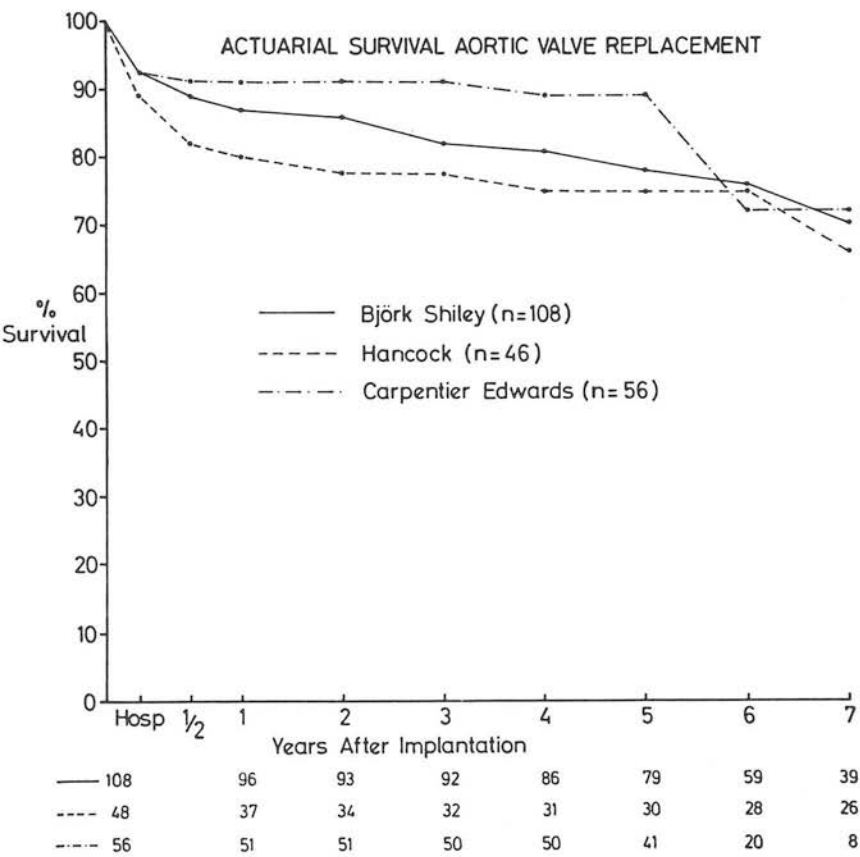
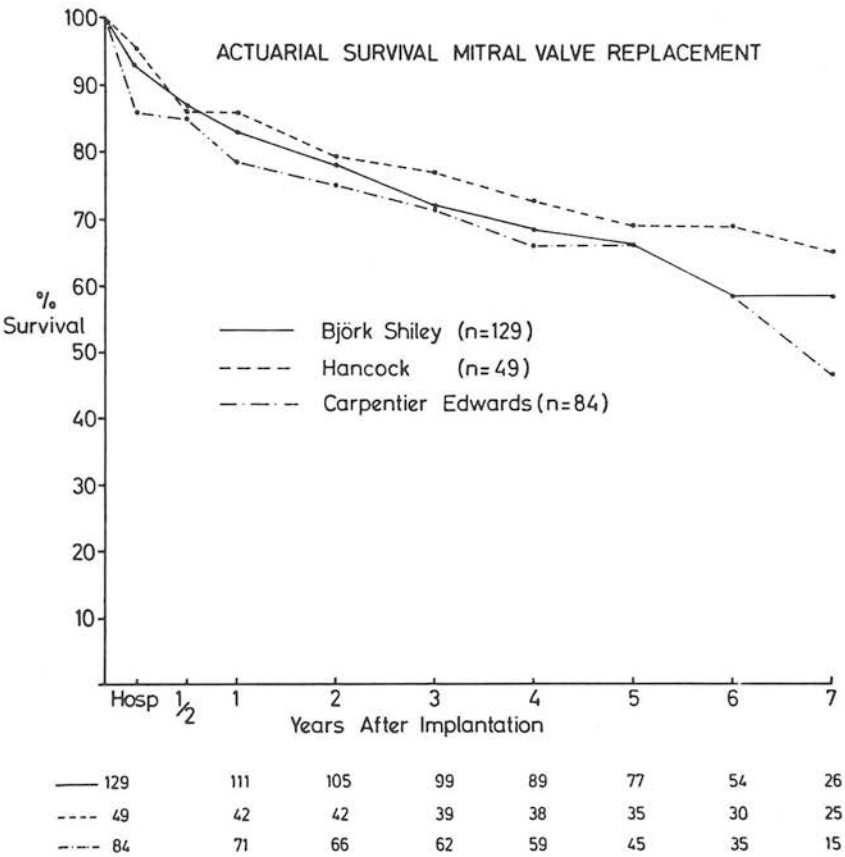


FIGURE 2.3

Edinburgh Heart Valve Study: Results at 5 Years

Actuarial survival curves for patients undergoing mitral valve replacement with each type of prosthesis used.



prosthetic valves. The results among mitral valve replacement patients showed no significant differences in incidence of embolism with use of the three prostheses. A mean of  $58.5 \pm 5.2\%$  of Bjork-Shiley valve patients were alive and  $48.8 \pm 9.2\%$  were alive and free from embolism at seven years. For Hancock valve patients, values were  $65.3 \pm 7.8\%$  and  $49.3 \pm 8.1\%$  respectively, and for Carpentier-Edwards patients values were  $46.4 \pm 7.8\%$  and  $39.2 \pm 8.8\%$  respectively (Figure 2.4).

The incidence of embolism following aortic valve replacement was less than with mitral valve replacement ( $p = 0.005$ ), and statistical analysis again showed no differences in incidence with use of the three prostheses. A mean  $70.4 \pm 6.1\%$  of Bjork-Shiley valve patients were alive and  $66.1 \pm 6.2\%$  were alive and free of embolism after seven years. For Hancock valve patients, values were  $66.6 \pm 12.1\%$  and  $56.3 \pm 8.3\%$ , respectively, and for Carpentier-Edwards valve patients, values were  $71.9 \pm 9.5\%$  and  $52.3 \pm 14\%$  (Figure 2.5).

The relationship between use of anticoagulants and the incidence of thromboembolism is shown in Table 2.4. Because of the variable anticoagulant policy for patients with porcine valves during the study, the total number of patient-years of treatment with and without anticoagulants was calculated for each treatment group, and the incidence of embolism was expressed as a ratio of emboli per 100 patient-years of exposure. Actuarial analysis was also performed. There was no significant difference in the incidence of embolism between those treated with and

FIGURE 2.4

Edinburgh Heart Valve Study: Results at 5 Years

Actuarial survival and survival free from embolism for patients undergoing mitral valve replacement with the three prostheses.

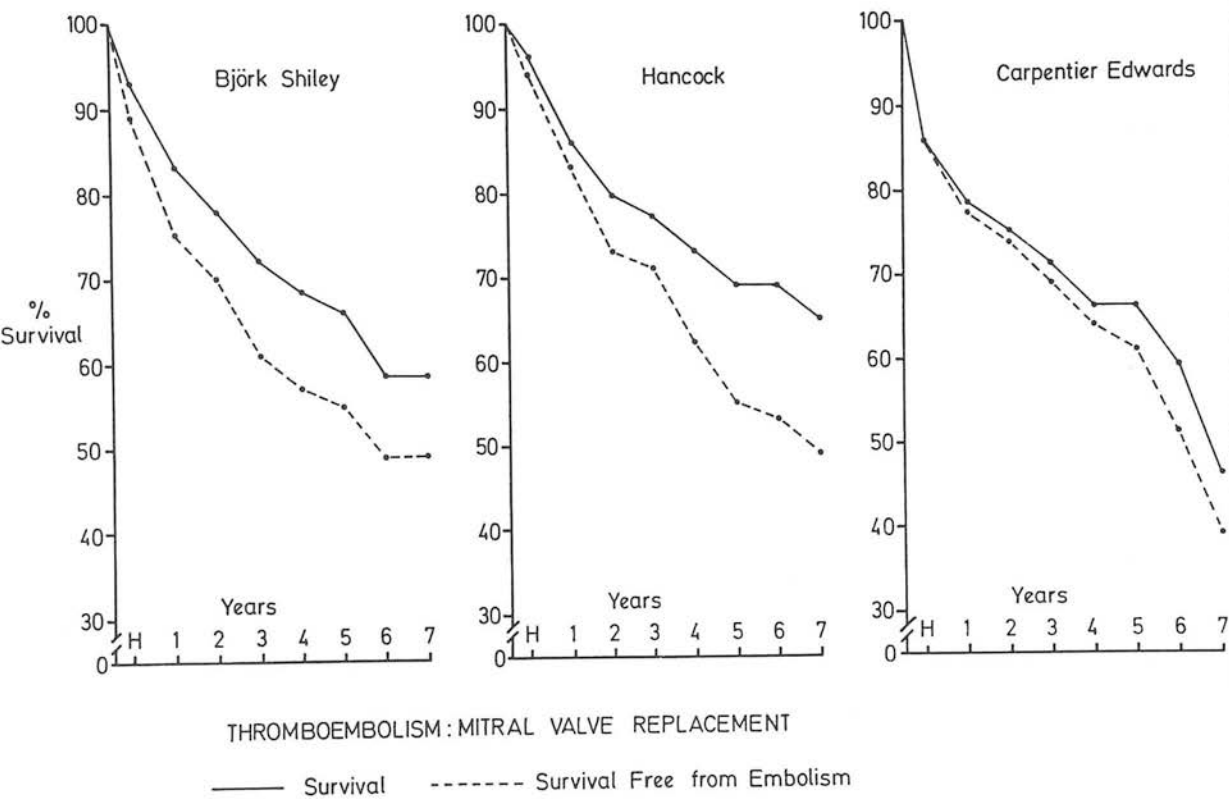
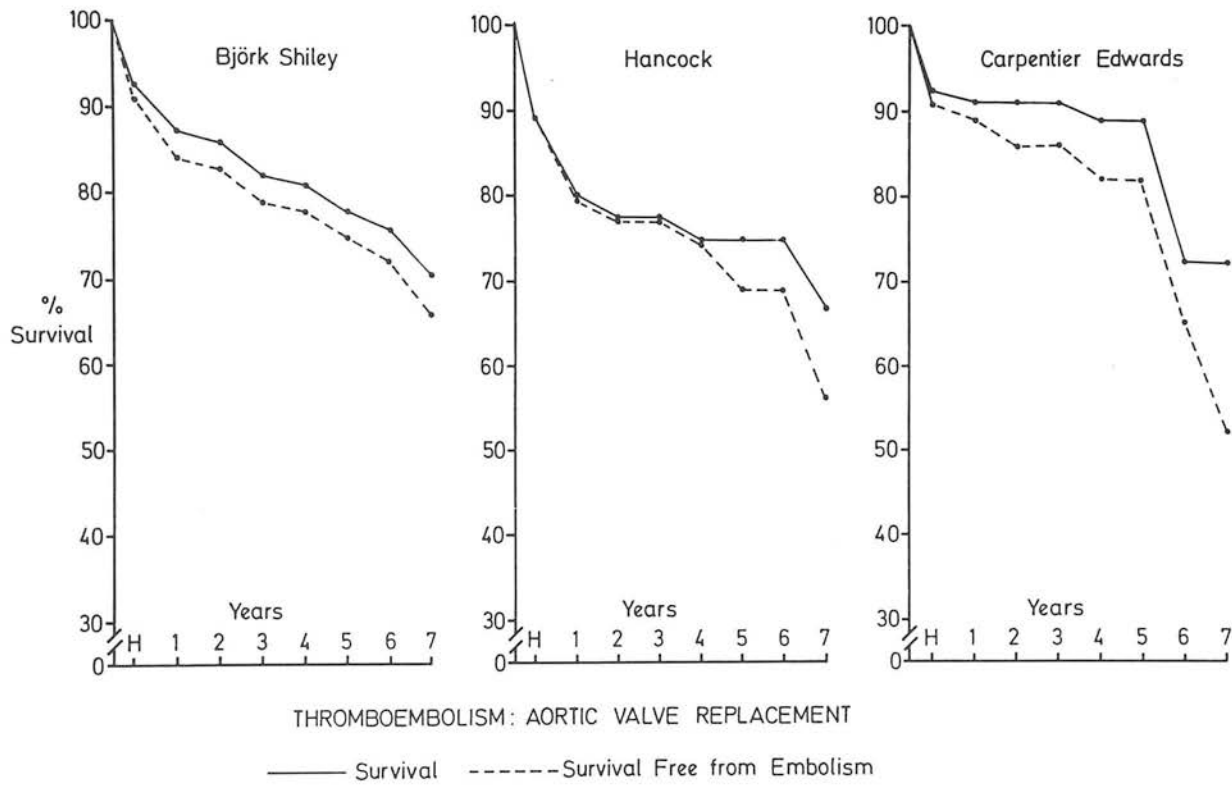




FIGURE 2.5

Edinburgh Heart Valve Study: Results at 5 Years

Actuarial survival and survival free from embolism for patients undergoing aortic valve replacement with the three prostheses.



without anticoagulants.

Factors affecting the incidence of thromboembolism were sought by multiple regression analysis of preoperative and postoperative variables. Age less than 65 years ( $p < 0.01$ ) and rheumatic etiology ( $p < 0.01$ ) were associated with embolism in patients whose aortic valves were replaced. For recipients of mitral valve prostheses, only atrial fibrillation predicted embolism ( $p < 0.001$ ; Table 2.4). Overall, only 78 of 262 patients with replaced mitral valves remained in sinus rhythm, and eight of the 78 had emboli. Only two patients with bioprosthetic mitral valve replacements and sinus rhythm had emboli.

Two patients died as a result of complications of anticoagulation, and a further 16 patients had significant complications from treatment. The number of complications was similar for the three prostheses, with an overall event rate of 1.3 per 100 patient-years.

### **Discussion**

In this study, the randomization process resulted in the equal distribution of 34 preoperative clinical variables, many of which are known to influence early and late outcome following valve replacement. These include age, sex, valvular lesion, functional class, electrocardiographic evidence of left ventricular hypertrophy, radiographic evidence of cardiomegaly, pulmonary artery pressure, left ventricular end-diastolic pressure, and the presence of associated coronary artery disease. In addition, the three participating surgeons were equally represented in the three treatment groups.

TABLE 2.4

## EDINBURGH HEART VALVE STUDY. RESULTS AT FIVE YEARS

## INCIDENCE OF EMBOLI IN PATIENTS TREATED AND THOSE NOT TREATED WITH ANTICOAGULANTS

	Atrial fibrillation	No. of emboli	Fatal emboli or residual	Patient-years of treatment	Emboli per 100 patient years
<b>Aortic valve replacement</b>					
Bjork-Shiley + anticoagulants (100)		7	0	498	1.41
Hancock + anticoagulants (7)		1	1	39	2.56
Carpentier-Edwards + anticoagulants (8)		1	0	48	2.08
Hancock, no anticoagulants (34)		5	3	173	2.90
Carpentier-Edwards, no anticoagulants (45)		4	1	201	1.99
<b>Mitral valve replacement</b>					
Bjork-Shiley + anticoagulants (122)	91	25	12	499	5.01
Hancock + anticoagulants (16)	13	1	1	90	1.11
Carpentier-Edwards + anticoagulants (20)	14	3	1	85	3.53
Hancock, no anticoagulants (30)	16	8	2	157	5.10
Carpentier-Edwards, no anticoagulants (51)	31	7	3	242	2.89

P = NS

P = NS

\* Numbers in parentheses are initial numbers of patients in each group

The majority (88.3%) of patients available for the trial were included in it, with only a minority of patients excluded on the basis of well-defined criteria. For these reasons the treatment groups appeared to be well randomized and representative of the population studied, and any difference in outcome should reflect the influence of the prosthesis concerned.

The design of the trial was compromised by a change in the porcine prosthesis used (from the Hancock to the Carpentier-Edwards model) after 14 months. The possibility that time of operation might bias the results was examined by analysing the results of Bjork-Shiley valve replacement in the first 14 months and in the later part of the trial. No difference in results was detected, so the results of Bjork-Shiley valve replacement in the first 14 months and in the later part of the trial were combined. The change in prosthesis used unfortunately resulted in fewer patients with Hancock prostheses being followed for a longer period, and a larger number with Carpentier-Edwards prostheses being followed for a shorter period.

Actuarial survival curves showed no significant difference for the three prostheses either overall or for aortic, mitral, or aortic plus mitral valve replacements.

For patients with mitral valve replacements, atrial fibrillation was the only predictor of thromboembolism and for those with aortic valve replacements, only age less than 65 years and rheumatic etiology (when associated mitral valve disease was commonly present) predicted thromboembolism. There was no difference in the incidence

of embolism with the three prostheses even though anticoagulation policy varied. For patients receiving porcine prostheses, anticoagulants were given in 19% of patient-years following aortic valve replacement, and in 30% for mitral valve replacement. The effect of anticoagulation with porcine prostheses was difficult to assess because of the varying and non-randomized policy on anticoagulation, but there was no evidence of any beneficial effect with aortic valve replacement. For patients with a Hancock prosthesis for mitral valve replacement, there was a lower incidence of embolism on anticoagulants, but this was not statistically significant, possibly reflecting the smaller numbers in this group. There was no evidence of benefit with anticoagulation in patients with Carpentier-Edwards mitral valve replacements.

#### **The Veterans Administration Cooperative Study on Valvular Heart Disease**

This study was designed to address two principle goals. The first was to compare survival and valve related complications between patients receiving the Bjork-Shiley mechanical and the Hancock porcine prostheses. The second was to assess the capability of a variety of clinical, haemodynamic, and angiographic variables to predict survival in patients with medically and surgically treated valvular heart disease, but to date no data pertaining to this has been published. The first aim of the study was identical to that of the Edinburgh study, and the design was similar.

## **Patients**

All male patients undergoing valve surgery for replacement of a single heart valve were considered for entry to the randomized trial. Informed consent was sought from all patients and only those for whom anticoagulants could be given were considered eligible for the trial. As in the Edinburgh study randomisation took place in the operating theatre, if there was no surgical reason to prefer one type of prosthesis. Patients with active endocarditis were excluded. During the five year study period 1078 patients underwent valve replacement and 575 who required single valve replacement were randomized.

## **Results**

Three hundred and ninety four patients underwent aortic valve replacement and 181 mitral valve replacement. Analysis of multiple clinical characteristics showed the patients to be well randomized between the two treatment groups.

### **Late Post-operative Deaths**

Of the 531 patients leaving hospital 13 patients withdrew or were lost to follow-up, but survival data was available on all patients. The mean duration of follow-up was 5 years (range 3 to 8 years). There were 186 late deaths during this follow-up period, 88 in patients receiving the Hancock prosthesis and 98 in those receiving the Bjork-Shiley mechanical prosthesis. Of these deaths 39 and 50 were due to non-cardiac causes in the Hancock and Bjork-Shiley groups respectively.

### **Reoperation for Valve Failure**

Details of the 31 patients who underwent valve rereplacement are shown in Table 2.5. There was no significant difference in the need for valve re-replacement in patients in the two groups. Reoperation for periprosthetic leak was more common after mechanical mitral valve replacement. In six patients undergoing aortic valve replacement (five who received the Hancock prosthesis) the randomized valve was changed at the initial operation because it could not be seated properly. No patient required reoperation for primary valve failure.

### **SURVIVAL**

#### **Aortic Valve Replacement**

There was no difference in actuarial survival between prostheses in those patients undergoing aortic valve replacement. Actuarial survival at 5 years was  $72 \pm 3\%$  for those receiving the mechanical prosthesis and  $70 \pm 4\%$  for those receiving the bioprosthesis (Figure 2.6).

#### **Mitral Valve Replacement**

There was a non-significant trend towards improved survival in patients undergoing mitral valve replacement with a bioprosthesis (29 deaths) compared with those receiving a mechanical prosthesis (40 deaths). Actuarial survival at 5 years was  $58 \pm 6\%$  for those receiving the mechanical prosthesis and  $70 \pm 5\%$  for those receiving the bioprosthesis (Figure 2.7).

#### **Valve Related Complications**

Results for survival free from any valve related complication were quoted independently of survival i.e.

TABLE 2.5

VA STUDY: REASONS FOR REPEAT OPERATION ON RANDOMIZED VALVE PROSTHESES

	Aortic Position		Mitral Position					
	Mechanical (n = 198)	Bioprosthesis (n = 196)	Mechanical (n = 88)	Bioprosthesis (n = 93)				
	N	(%)	N	(%)	N	(%)		
Endocarditis	2	(1.0)	1	(0.5)	1	(1.1)	2	(2.2)
Valve thrombosis	1	(0.5)	0	(0)	1	(1.1)	0	(0)
Regurgitation								
Central valvular	0	(0)	0	(0)	0	(0)	0	(0)
Perivalvular	4	(2.0)	4	(2.1)	6	(6.8)	1	(1.1)
Valve change during initial operation	1	(0.5)	5	(2.6)	0	(0)	0	(0)
Other	1	(0.5)*	0	(0)	0	(0)	1	(1.1)+
Total	9	(4.5)	10	(5.1)	8	(9.1)	4	(4.3)

\*Anticoagulant-related haemorrhage. + Repair of left ventricular to right atrial shunt 3 months after initial operation; prosthetic valve was changed even though it was normal



FIGURE 2.6

Veterans Administration study: actuarial survival of patients undergoing aortic valve replacement comparing those receiving a bioprosthesis (Bio) with those receiving a mechanical prosthesis (Mech). The numbers adjacent to the points at 2, 4 and 6 years are the numbers of patients available for observation at that time and the vertical bars indicate one standard-error of survival probability (prob).

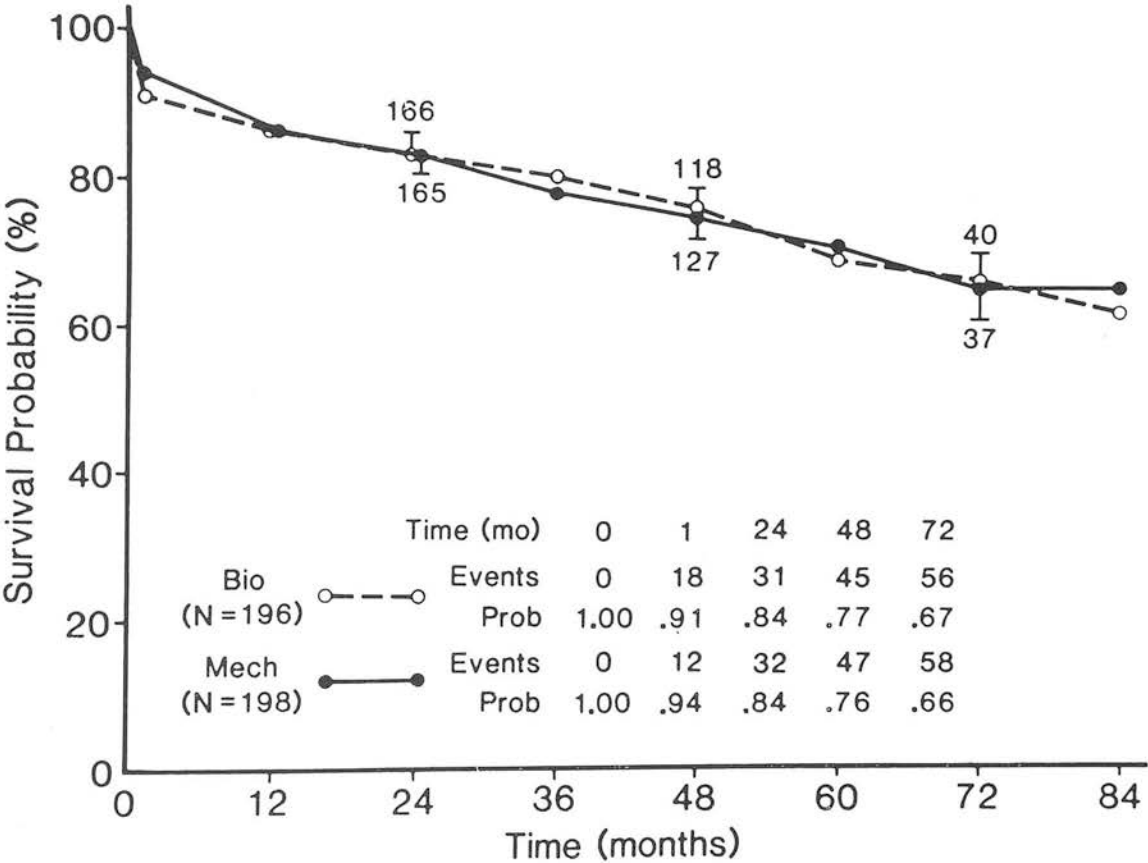
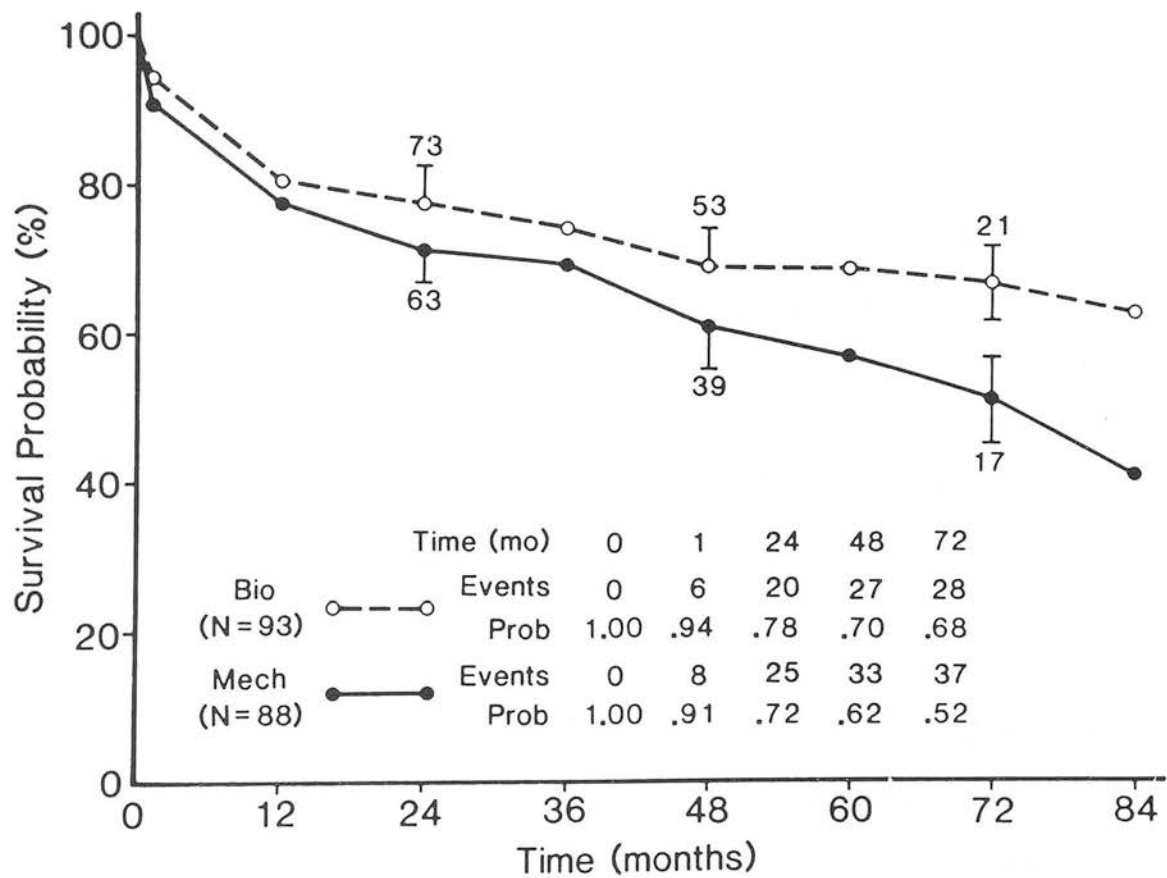


FIGURE 2.7

Veterans Administration study: actuarial survival of patients undergoing mitral valve replacement comparing those receiving a bioprosthesis with those receiving a mechanical prosthesis. Format and abbreviations as in Fig 2.6.



those dying from a different cause without having developed a valve related complication, were removed from the analysis. Where the death was clearly or possibly related to the prosthetic valve this was counted as a fatal valve-related complication. Only the first event was considered for actuarial analysis. In the Edinburgh study actuarial survival, and survival free from thromboembolism were presented.

### **Embolism**

#### **Aortic Valve Replacement**

The total number of embolic episodes was greater in patients with a bioprosthesis (20 episodes) compared with a mechanical prosthesis (15 episodes). More patients with a bioprosthesis had more than one embolism and actuarial freedom from embolism at five years was  $92 \pm 2\%$  for patients with a mechanical prosthesis and  $91 \pm 2\%$  for patients with a bioprosthesis.

#### **Mitral Valve Replacement**

Systemic embolism occurred with equal frequency in both groups and actuarial freedom from embolism at five years was  $89 \pm 4\%$  for patients with a mechanical prosthesis and  $91 \pm 3\%$  for patients with a bioprosthesis.

### **Bleeding**

In the total group of patients 146 episodes of bleeding occurred of which 17 were fatal. (In the Edinburgh study only 18 episodes occurred two of which were fatal). For patients undergoing aortic valve replacement actuarial freedom from bleeding was  $67 \pm 4\%$  for those with a mechanical prosthesis and  $85 \pm 3\%$  for those with a

bioprosthesis. For patients undergoing mitral valve replacement actuarial freedom from bleeding was  $64 \pm 7\%$  for those receiving a mechanical prosthesis and  $88 \pm 4\%$  for those receiving a bioprosthesis.

### **All Valve Related Complications**

When all valve related complications i.e. bleeding, embolism, reoperation and bacterial endocarditis were considered together, there was a significant difference between the two prostheses for patients undergoing both aortic and mitral valve replacement. For aortic valve replacement probability of freedom from fatal or non fatal valve related complication at 5 years was  $53 \pm 4\%$  for those receiving a mechanical prosthesis and  $63 \pm 4\%$  for those receiving a bioprosthesis. Corresponding figures for mitral valve replacement at 5 years was  $45 \pm 6\%$  for those receiving a mechanical prosthesis, and  $67 \pm 5\%$  for those receiving a bioprosthesis. These differences were almost entirely due to the difference in bleeding complications.

### **Comparison between the Edinburgh and VA Trials**

The patient populations enrolled in the two studies differed in several ways. All the patients in the VA study were male, but 78%, 29%, and 67% of those undergoing mitral, aortic, and combined valve replacements respectively in the Edinburgh study were female. The Edinburgh patients were younger, less symptomatic and had a much lower incidence of documented coronary artery disease (Table 2.6). Survival and incidence of reoperation was similar in the two studies (Table 2.7). An exception was survival in patients receiving the mechanical prosthesis in

TABLE 2.6

## COMPARISON OF BASELINE CHARACTERISTICS BETWEEN THE VETERANS ADMINISTRATION AND EDINBURGH STUDIES

Variable	Percent of Patients			
	Aortic Valve Replacement		Mitral Valve Replacement	
	Edinburgh (n = 210)	VA (n = 394)	Edinburgh (n = 262)	VA (n = 181)
Age (yr)				
< 50	29	11	34	15
50 to 65	53	63	55	70
> 65	17	26	12	14
Functional class				
I, II	53	29	41	12
II, IV	47	70	59	87
Valve lesion				
Stenosis	30	51	30	36
Regurgitation	26	24	12	39
Stenosis/regurgitation	46	25	58	26
Coronary disease	8.6	44	5.3	41
Prior valvotomy	-	-	52	13

VA = Veterans Administration

TABLE 2.7

## COMPARISON OF RESULTS AT FIVE YEARS OF VETERANS ADMINISTRATION AND EDINBURGH RANDOMIZED TRIALS

Number	Aortic Valve Replacement				Mitral Valve Replacement					
	Edinburgh	H	CE	VA	Edinburgh	H	CE	VA		
Operative mortality (%)	7.4	11	5.4	6.1	9.2	5.4	6.1	16	9.1	6.5
7 Year Survival probability	.70	.67	.72	.66	.63	.59	.65	.46	.42	.64
Emboli (% of patients)	7.0	15	9.4	6.6	9.2	20	20	14	9.1	9.7
Reoperation (% of patients)	4.6	8.7	1.8	4.5	5.1	5.4	10	7.1	9.1	4.3

BS = Bjork-Shiley valve; CE = Carpentier-Edwards porcine heterograft valve;  
H = Hancock porcine heterograft valve; VA = Veterans Administration

the mitral position; seven year probability of survival was lower in the VA patients (42%) than in the Edinburgh patients (59%), Table 2.7. The major difference in results between the two trials was the much higher incidence of valve related complications in patients receiving the mechanical prosthesis as against those receiving the bioprosthesis in the VA study. This difference was almost entirely due to an increased risk of bleeding in patients receiving the mechanical prosthesis, compared with those receiving the bioprosthesis.

Why was the risk of bleeding so much higher in the VA study? The definition of bleeding in the VA study included all patients requiring a blood transfusion for any reason. This group included those with haematuria requiring hospitalisation and many of these patients underwent transurethral resection of the prostate, a common operation in an aging male population. Indeed, there were a total of 40 episodes of bleeding recorded for patients with a bioprosthesis only half of whom were taking anticoagulants at the time. It was possible that bleeding complications were more accurately recorded in the prospectively collected data in the VA study in which all patients were seen by one of the investigators, or his assistant, every 6 months. It was also possible that the therapeutic range of warfarin control in the VA study was too high. The protocol in the VA study specified a prothrombin ratio of 2.0-2.5 times the control level. In the USA the prothrombin time is most commonly estimated using commercial preparations based on rabbit brain

thromboplastin, whereas in the UK this is based on a centrally standardised human brain thromboplastin which is more sensitive. The prothrombin ratio of 2.0-4.0 used in the Edinburgh study is equivalent to a ratio of 1.3-1.8 or 1.3-2.0 in the USA, depending on the commercial reagent used. A therapeutic ratio of 2.0-2.5 in the USA would be considered excessive in the UK. This discrepancy has recently been appreciated in the USA (Hirsch 1987) and latterly the therapeutic range recommended in the VA study has been reduced to 1.5-2.0. Furthermore many of the patients in the Edinburgh Valve Trial had their anticoagulant control monitored at an anticoagulant clinic, a practice not often adopted in the USA, but one which appears to improve anticoagulant control (Petty et al 1988).

It was clear that if major differences in durability between prostheses was to emerge then follow-up would need to be extended. Complications of anticoagulant treatment and indeed, all episodes of bleeding needed to be recorded accurately for all patients rather than simply relying on routine clinical review. It was, therefore, decided to design a specific questionnaire for all surviving patients in the Edinburgh study to determine if any episodes of bleeding or blood transfusion had passed undetected by our usual methods of review. The results of this work up to a mean follow-up of 10.5 years is presented for survival and reoperation in Chapter 3, and for thromboembolism and complications of anticoagulation in Chapter 4.



### CHAPTER 3

#### **RESULTS OF THE EDINBURGH HEART VALVE TRIAL AT TEN YEARS: SURVIVAL AND REOPERATION**

In the 1980's it became apparent that bioprosthetic valves might have limited durability in adult patients as well as in children and adolescents. Degeneration of bioprosthetic valves is more common six or more years after valve replacement (Foster et al 1987). In consequence we anticipated that follow-up of patients in the Edinburgh trial for more than 5 years after operation might show differences in survival between patients with the Bjork-Shiley mechanical and the Hancock and Carpentier-Edwards bioprostheses.

#### **Patients and Methods of Analysis**

These were as described in Chapter 2. In order to be sure that no valve-related complications were missed a questionnaire was sent to all surviving patients as described in Chapter 4. Deaths occurring following hospital discharge after initial valve replacement were classified as "cardiac", "non-cardiac" or "possibly cardiac" on the basis of stated clinical data, information gathered at autopsy. In addition information from the death certificate lodged with the Registry of Deaths for Scotland was available for patients whose death occurred in Scotland (more than 90%). Deaths of those patients undergoing prosthetic valve replacement who died at reoperation were recorded as prosthesis-related deaths.

Statistical analysis was as described in Chapter 2. Results were analysed and presented in a manner similar to

those for the VA cooperative study in valvular heart disease; this facilitated comparison of the two studies. Overall survival and actuarial survival free from any of the valve related complications described in Chapter 2 were compared within the treatment groups. Only the first valve related complication was considered for an individual patient. A patient undergoing reoperation for prosthetic valve replacement was no longer included for other valve related complications but continued to be included for survival analysis. Patients undergoing cardiac surgery for reasons other than replacement of the randomised valve were followed for all events.

## RESULTS

The treatment groups were previously shown to be well randomised although the randomisation process was potentially compromised by the change in the type of porcine prosthesis used after the trial had commenced. This introduced the possibility that the time of operation might bias results although it had been shown after 5 years of follow-up that the results of Bjork-Shiley valve replacement were not significantly different during the early and late periods of the trial. The use of two types of porcine bioprosthesis resulted in 107 patients receiving the Hancock prosthesis, and a larger group of 160 patients receiving the Carpentier-Edwards prosthesis who were followed for a shorter period of time. Analysis was performed for separate periods of the trial, for both porcine valves grouped together and for each porcine valve separately. The aim of the trial was to compare long-term

results between the mechanical and porcine prostheses and for this reason actuarial results are presented comparing the Bjork-Shiley prosthesis with both porcine prostheses considered together and also with the Hancock and Carpentier-Edwards prostheses considered separately.

Of the 540 patients randomised 8 received tricuspid valve replacement and were excluded from further analysis. All surviving patients were followed at least until September 1987. The mean duration of follow-up was 10.5 years with a range of 7.5 to 12.5 years. Eight patients were lost to follow-up.

## **SURVIVAL**

### **Late post operative deaths**

Of the 532 patients included for analysis 44 died before leaving hospital and there were 201 late deaths including those following reoperation. The causes of death (cardiac, possibly cardiac, non cardiac or not known) are categorised in Table 3.1. The cardiac deaths were further divided into those that could and could not be attributed to the prosthesis but since autopsy was performed on less than 50% of patients who died this information is incomplete and is not presented. Most cases of possible cardiac death were sudden and information from an autopsy was not usually available.

### **Actuarial Survival**

**All patients** Analysis of actuarial survival for all patients in the study showed no significant difference between those with the Bjork-Shiley, Hancock and Carpentier-Edwards prostheses up to 10.0 years of follow-up

TABLE 3.1

CAUSES OF ALL LATE POST OPERATIVE DEATHS

	Bjork (n=266)	Porcine (n=266)	Hancock (n=107)	Carpentier (n=159)
Cardiac Death	62	52	25	27
Possible Cardiac Death	12	22	8	14
Non-cardiac Death	23	25	13	12
Not Known	2	3	1	2
Total	99	102	47	55

Total Late Deaths = 201

(Figure 3.1). This applies when the latter groups were considered separately and together. Actuarial survival for all patients was  $56.5 \pm 2.2\%$  at 10.0 years.

#### **Aortic valve replacement**

Analysis of actuarial survival for patients undergoing aortic valve replacement showed no significant difference between those with the Bjork-Shiley or the porcine prostheses whether these were considered separately or together. Actuarial survival for all patients undergoing aortic valve replacement was  $65.2 \pm 3.3\%$  at 10 years (Figure 3.2)

#### **Mitral valve replacement**

Analysis of actuarial survival for patients undergoing mitral valve replacement showed no significant difference between those with the Bjork-Shiley or the porcine prostheses whether these were considered together or separately. Actuarial survival for all patients undergoing mitral valve replacement was  $50.1 \pm 3.2\%$  at 10 years (Figure 3.3).

#### **Mitral and aortic valve replacement**

Analysis of actuarial survival for patients undergoing combined mitral and aortic valve replacement showed no significant difference between those with the Bjork-Shiley or the porcine prostheses considered separately or together, but this subgroup comprised only 60 patients.

#### **Late post operative events**

Thromboembolism, bleeding requiring hospitalisation or transfusion, bacterial endocarditis and reoperation for prosthetic valve replacement were all considered significant events. Reoperation is discussed in this chapter and the other events are discussed in chapter 4.

FIGURE 3.1

Edinburgh Heart Valve Study: Results at 10 Years

Actuarial survival for all patients undergoing valve replacement.

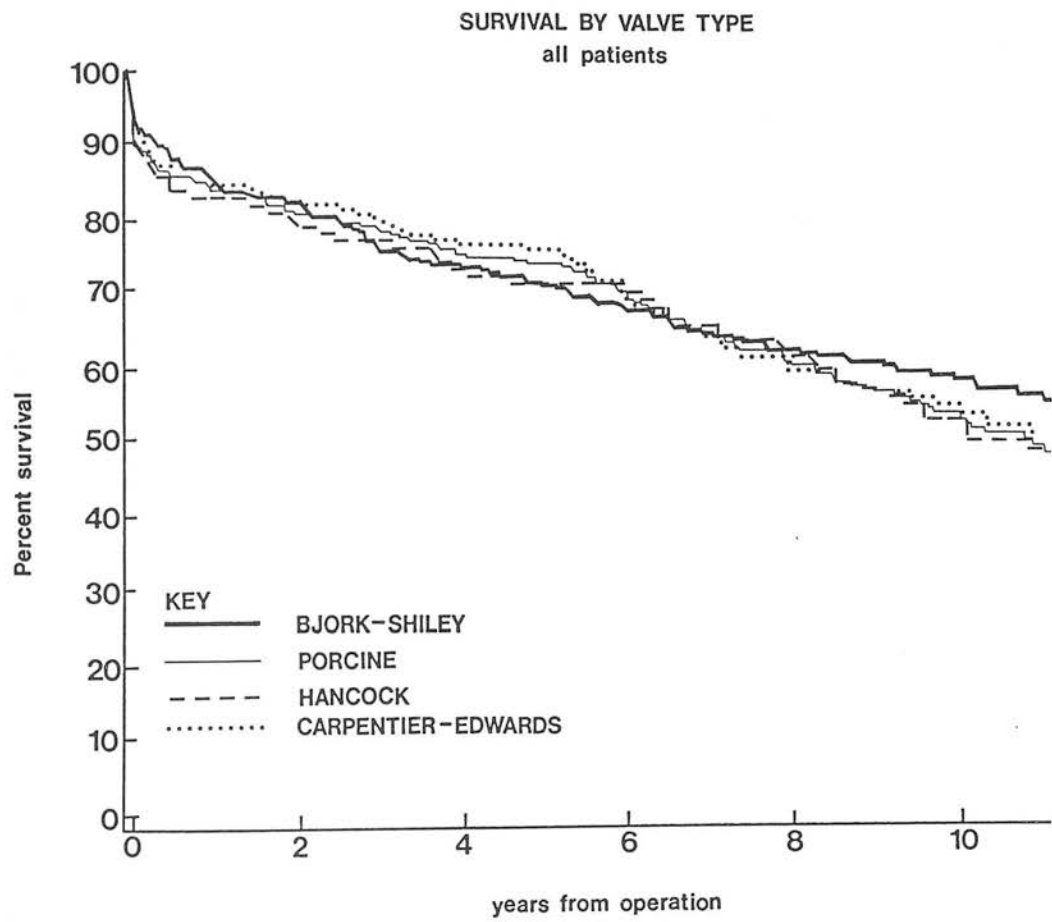


FIGURE 3.2

Edinburgh Heart Valve Study: Results at 10 Years

Actuarial survival for patients undergoing aortic valve replacement.

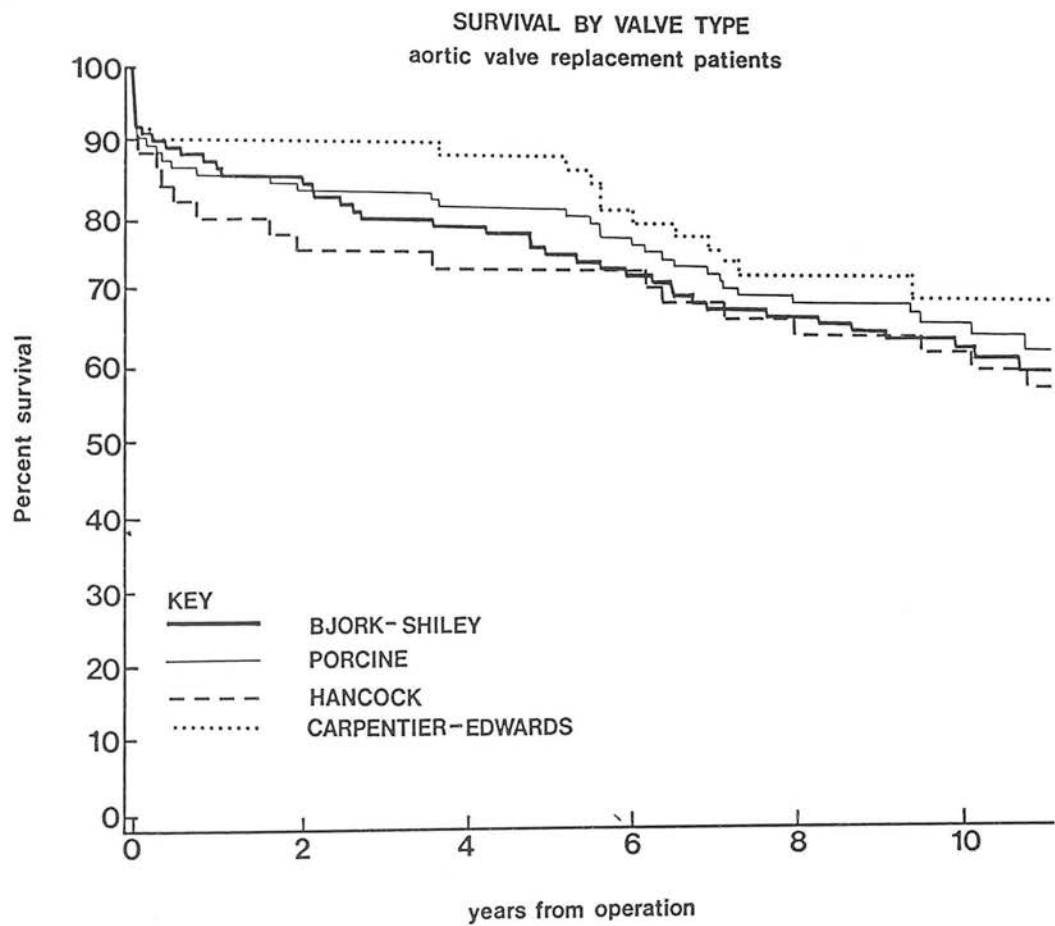
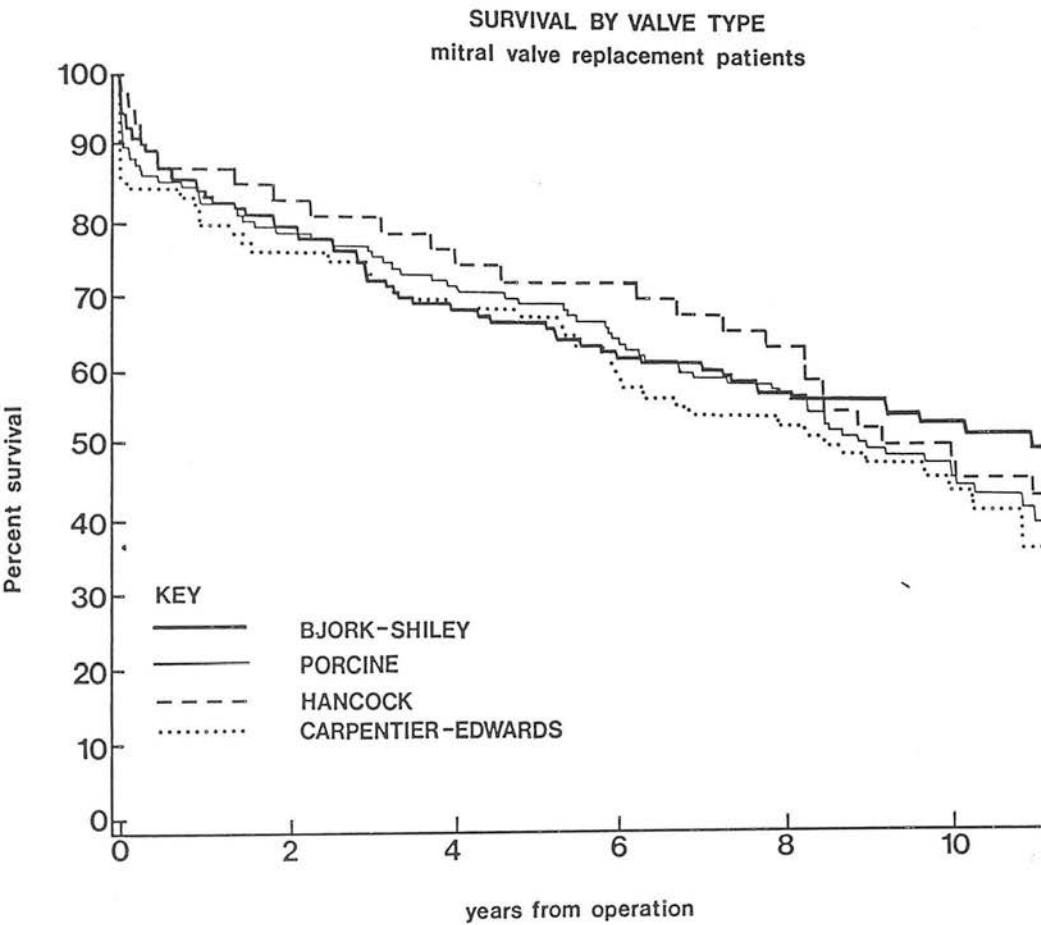


FIGURE 3.3

Edinburgh Heart Valve Study: Results at 10 Years

Actuarial survival for patients undergoing mitral valve replacement.





## REOPERATION

Seventy patients have undergone reoperation to replace the randomised prosthetic valve; 17 with the Bjork-Shiley, and 53 with porcine prostheses (20 with Hancock and 33 with Carpentier-Edwards prostheses). Sixteen patients undergoing reoperation died before hospital discharge. Of the 54 patients successfully undergoing reoperation 16 have subsequently died. Reoperation was significantly more frequent after porcine aortic valve replacement and porcine mitral valve replacement. When the two types of porcine prostheses were considered separately reoperation was significantly more frequent after Hancock aortic valve replacement and Carpentier-Edwards mitral valve replacement. These differences were almost exclusively due to reoperation required because of leaflet failure of the porcine valves occurring more than five years after implantation (Table 3.2). Of the eleven patients who had undergone combined aortic and mitral valve replacement with Hancock or Carpentier-Edwards prostheses nine required reoperation because of leaflet failure; the aortic prosthesis had failed in 2 patients, the mitral in 5 and both prostheses had failed in 2 patients.

### Actuarial analysis

Degeneration of porcine prostheses might be gradual and failure of a mechanical prosthesis might be abrupt and catastrophic (Taylor 1988). The number of patients undergoing reoperation for failure of a porcine prosthesis in this study might possibly have been offset by a similar number of patients with Bjork-Shiley prostheses dying

TABLE 3.2

NUMBER OF PATIENTS (NUMBER IN EACH GROUP) UNDERGOING REOPERATION

Prosthesis	AVR	MVR	AVR+MVR	Total	>5 years after initial operation
Bjork-Shiley (n=266)	4(108)	9(129)	4(29)	17	4
Porcine (n=266)	12(102)*	30(132)**	11(31)**	53**	42**
Hancock (n=107)	9(46)**	7(49)	4(12)	20	14 **
Carpentier-Edwards (n=266)	3(56)	23(84)**	7(19)	33	28 **
Total (n=532)	18(210)	39(232)	15(60)	70	46

\* p = <0.05 \*\* p = <0.01 compared to Bjork-Shiley group

suddenly due to prosthetic failure. Therefore, we examined actuarial survival free from reoperation and from all classifications of cardiac death to determine if there was a difference in the rate of occurrence of prosthetic valve failure.

#### **Actuarial Survival Free From Reoperation Or Cardiac Death**

**All Patients.** Actuarial survival free from reoperation or cardiac death showed a significant difference favouring the Bjork-Shiley prosthesis when compared with both porcine prostheses considered together ( $p=0.02$ ), and when the Hancock and Carpentier-Edwards prostheses were considered separately ( $p=0.05$ ) (Figure 3.4).

#### **Aortic Valve Replacement**

Actuarial survival free from reoperation or cardiac death for the subgroup of patients undergoing aortic valve replacement was not different when patients receiving the Bjork-Shiley prosthesis were compared with those receiving the Hancock or Carpentier-Edwards porcine prostheses considered together. If these latter groups were considered separately there was a higher actuarial survival free from reoperation or cardiac death in those receiving the Carpentier-Edwards prosthesis than those receiving the Bjork-Shiley prosthesis, but this did not reach statistical significance ( $p = 0.07$ ) (Figure 3.5).

#### **Mitral Valve Replacement**

Actuarial survival free from reoperation or cardiac death for the subgroup of patients undergoing mitral valve replacement was higher for patients receiving the Bjork-Shiley prosthesis compared with those receiving a porcine

**FIGURE 3.4**

**Edinburgh Heart Valve Study: Results at 10 Years**

All patients undergoing valve replacement: actuarial survival with any classification of cardiac death or reoperation as the end point.

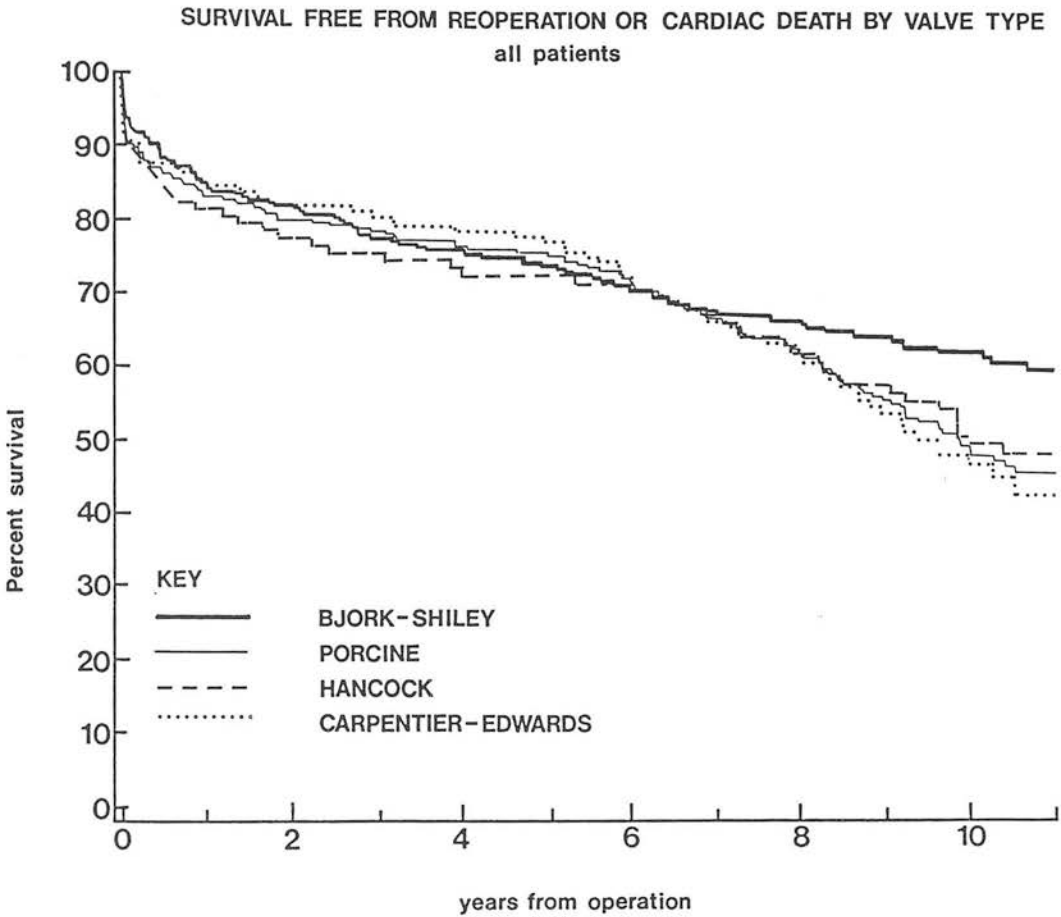
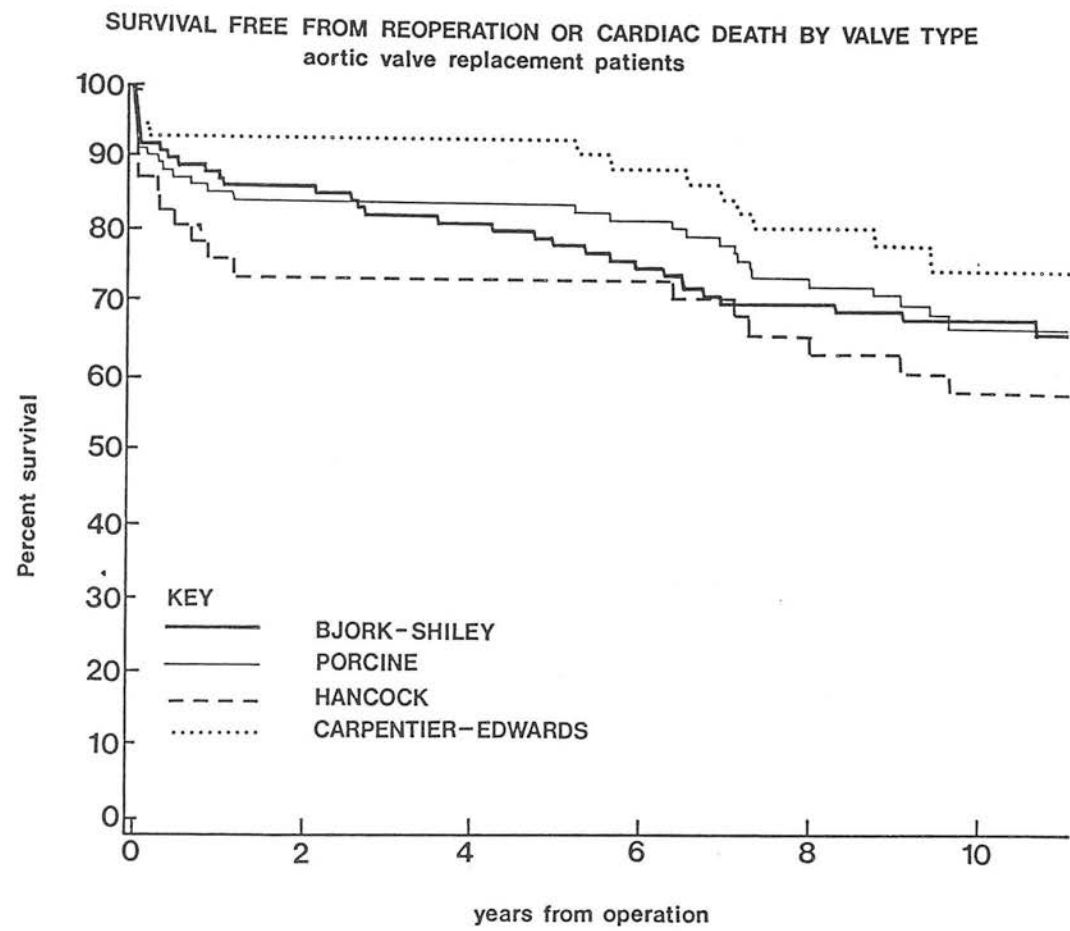


FIGURE 3.5

Edinburgh Heart Valve Study: Results at 10 Years

Patients undergoing aortic valve replacement: actuarial survival with any classification of cardiac death or reoperation as the end point.



prosthesis but this did not reach statistical significance ( $p = 0.06$ ). When those receiving the Carpentier-Edwards and the Hancock prosthesis were considered separately there was a significant difference between those receiving the Bjork-Shiley prosthesis and those receiving the Carpentier-Edwards prosthesis ( $p = 0.02$ ) but not those receiving the Hancock prosthesis (Figure 3.6).

## **Discussion**

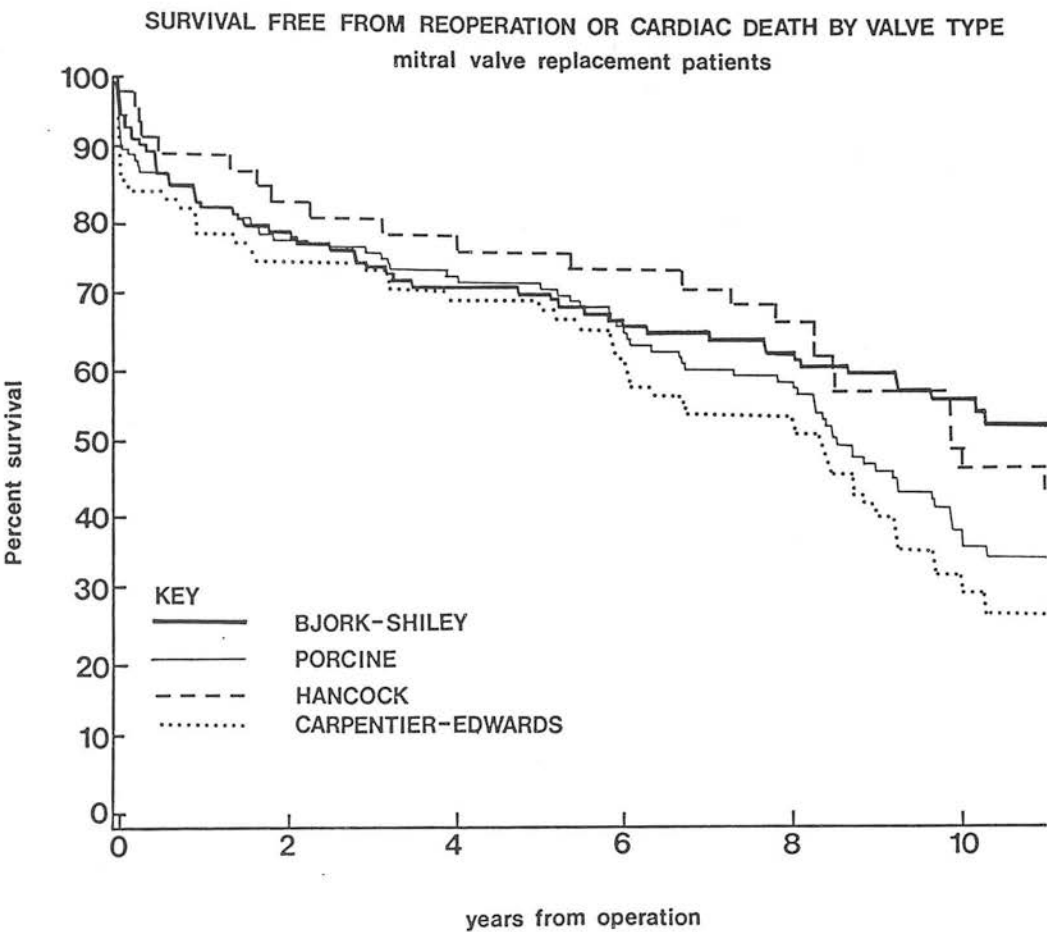
We have shown no difference in survival after a mean of 10.5 years of follow-up in patients receiving the Bjork-Shiley mechanical prosthesis and those receiving a Hancock or Carpentier-Edwards prosthesis in a large randomised prospective trial.

There was however a significant difference in the need for reoperation due to the increased incidence of porcine valve failure which occurred five or more years after implantation. Mechanical valve failure can on occasions occur suddenly causing death before the patient can be brought to surgery. In a few instances death was sudden and shown to be caused by prosthetic valve obstruction. In most instances of sudden death an autopsy was not performed and in many cases death was attributed to myocardial infarction. Some of these cases may have been due to sudden failure of the prosthetic valve. Failure of bioprosthetic valves is usually gradual and the patient is likely to come to reoperation and this may be the reason that more patients with bioprosthetic valves came to reoperation. To determine if this was the case we analysed actuarial survival free from reoperation and from all

FIGURE 3.6

Edinburgh Heart Valve Study: Results at 10 Years

Patients undergoing mitral valve replacement: actuarial survival with any classification of cardiac death or reoperation as the end point.



cardiac deaths. There was a significant difference in actuarial survival free from reoperation or cardiac death favouring those who received the Bjork-Shiley prosthesis when all patients undergoing valve replacement were considered. There was also a significant difference favouring the Bjork-Shiley prosthesis compared with the Carpentier-Edwards prosthesis for patients undergoing mitral valve replacement. For patients undergoing aortic valve replacement there was no significant difference in actuarial freedom from reoperation or cardiac death between those receiving the different prostheses. This indicates that the failure rate of the porcine valves was indeed significantly higher with the possible exception of those undergoing single aortic valve replacement.

Reoperation for failure of bioprosthetic valves was more common for those used in the mitral rather than the aortic position. Furthermore, in patients with both mitral and aortic bioprostheses when reoperation for valve failure was required it was twice as common for the mitral prosthesis to have failed. This is in agreement with findings previously noted by others (Bolooki et al 1983, Warnes et al 1983).

There appeared therefore to be a significant advantage to the Bjork-Shiley prosthesis with a lower incidence of late prosthetic failure and the need for reoperation when compared to the porcine prostheses. This advantage occurred most noticeably in patients undergoing mitral valve replacement, especially those in whom the Carpentier-Edwards prosthesis was used.



The main advantage of porcine prostheses is the lack of need for long-term anticoagulant treatment with the attendant risks of bleeding. The occurrence of bleeding and the other valve related events, embolism and bacterial endocarditis are presented in the next Chapter.

## **CHAPTER 4**

### **RESULT OF THE EDINBURGH HEART VALVE TRIAL AT 10 YEARS VALVE RELATED COMPLICATIONS**

In Chapter 3 we observed no difference in overall survival between patients undergoing valve replacement with a porcine or Bjork-Shiley mechanical valve prosthesis, but there was a noticeably increased risk of reoperation for those patients receiving porcine valve replacements compared with those receiving mechanical valve replacements. In this Chapter we consider complications that might have arisen in patients after their valve replacement operations in addition to reoperation; these include embolism, bleeding and complications with anticoagulants, and bacterial endocarditis. A brief review of the occurrence of embolism in association with valvular heart disease is given, and the occurrence of this and other valve related complications in patients in the Edinburgh heart valve trial is presented.

#### **Embolism**

It has long been established that there is an association between valvular heart disease and systemic embolisation. This association is strongest with mitral valve disease, especially in patients who have developed atrial fibrillation (Casella et al 1964; Coulshed et al 1970). Patients with mitral stenosis and in sinus rhythm remain at risk of systemic embolisation; at least 20% of emboli noted in 3 major series occurred in patients in sinus rhythm (Szekely 1964; Coulshed et al 1970; Fleming and Bailey 1971). Recently, it has been shown by

ambulatory monitoring that more than half of patients with mitral stenosis who are in sinus rhythm may have intermittent episodes of atrial arrhythmias which may be asymptomatic (Ramsdale et al 1987). Thrombus in various stages of organisation is frequently found in the left atrium in patients undergoing surgery for mitral valve disease (Ellis and Harken 1961). The development of thrombus in the left atrium has been thought to be due to stagnation of blood flow and the formation of eddy currents within an enlarged left atrium, which might be exacerbated by the diminished cardiac output common with mitral stenosis (Askey and Bernstein 1960).

There may be some diminution in size of the left atrium following mitral valve replacement but it commonly remains enlarged and we have observed significant left atrial enlargement was present in most patients who had undergone mitral valve replacement alone, or in combination with aortic valve replacement (see Chapter 6).

### **Clinical Manifestations of Systemic Emboli**

Large emboli causing stroke, or major damage to other organs or limbs produce obvious effects. Small emboli may cause no symptoms. It is common to find evidence of previous embolisation at autopsy in the kidneys of patients with valvular heart disease (Hoxie and Loggin 1940). The two organs in which small emboli are likely to cause symptoms are the brain and the retina, manifested as transient neurological deficit and amaurosis fugax. Such episodes may not be recorded at routine follow-up of patients with prosthetic valves attending for annual

review. McGoon (1984) noted the wide discrepancy in the incidence of systemic emboli following valve replacement, reported in several large series of patients. In reviewing the methods by which data was collected in 51 reported series he found that in many series specific information about possible episodes of embolism was not sought and information about anticoagulant treatment and the quality of its control was often omitted. Only rarely was follow-up data collected prospectively. The studies in which specific data was sought prospectively tended to report the higher incidence of systemic emboli and McGoon suggested specific guidelines for the collection of data related to embolism.

We have followed these guidelines and questions designed to detect any episode of embolism were included in the questionnaire which was sent, at two separate times of follow-up, to all surviving patients in the Edinburgh valve study. If an embolic episode was suspected from the patient's response to questionnaire then further information was sought from the patient directly and from his general practitioner.

### **Bleeding and Complications of Anticoagulation**

The major risk of prolonged systemic anticoagulation with warfarin is haemorrhage. Since the introduction of warfarin in 1941 its effects on various mechanisms in the clotting system have been elucidated, but the complete basis of the antithrombotic action of warfarin has not been fully understood. As Wessel and Gitel (1984) have noted "the dosage (of warfarin) was regulated according to the

prothrombin time, which predicted bleeding, rather than according to assays that demonstrated antithrombosis".

As discussed in Chapter 2 there was considerable difference in the thromboplastin used as the basis for testing the prothrombin time between the USA and the UK which, until recent times, has meant that patients treated with warfarin in the USA have been receiving higher doses than patients in the UK (Hirsch 1987; Lancet Editorial 1987). We have said that this could account for some of the discrepancies noted in the incidence of bleeding in the VA and the Edinburgh 5 years studies summarised in Chapter 2.

Other studies from the USA have not reported such a high incidence of haemorrhage as that noted in the VA study. Cohn reported on a series of 912 patients undergoing valve replacement surgery in Boston (also one of the larger geographical centres participating in the VA study) contemporaneously with those patients enrolled in the VA study. In Cohn's series the risk of haemorrhage was 1.82% per patient year, almost identical to the Edinburgh trial, but much lower than that of the VA study (6.6% for patients with the aortic mechanical prosthesis, 3.0% for patients with the aortic bioprosthesis, 7.2% for patients with the mitral mechanical prosthesis, and 2.4% for patients with the mitral bioprosthesis (Cohn 1984).

We have also noted that two other explanations for the discrepancy in rates of bleeding between the Edinburgh and VA studies could be due to differences in the definition of bleeding and also under-reporting of bleeding episodes in the Edinburgh study. Bleeding in the VA study was

essentially defined as an episode requiring hospitalisation or blood transfusion, but also included "gross haematuria leading to hospitalisation or urologic manipulation". In the aging male population studied there this included those undergoing prostatectomy whereas more than half of the patients enrolled in the Edinburgh study were female (Chapter 2). In the Edinburgh study we had not included clinical events requiring blood transfusion or haematuria unless these were related to anticoagulant treatment. To facilitate comparison of results in the two studies for later follow-up of patients, we therefore, amended the later questionnaire sent to all survivors and clearly defined bleeding as any episode necessitating blood transfusion or hospitalisation and asked patients to report any episodes of bleeding, or blood transfusion which had occurred at any time since their operation.

### **Bacterial Endocarditis**

Bacterial endocarditis was recorded if suspected clinically, or found at reoperation, or autopsy.

### **Statistical analysis**

Statistical analysis of results was performed as described in Chapter 3.

## **RESULTS**

### **Embolism**

There were a total of 113 episodes of embolism recorded in 91 patients. Fifty-nine embolic events occurred in 42 patients with Bjork-Shiley prostheses (28 undergoing mitral, 10 undergoing aortic and 4 mitral plus aortic valve replacement). Fifty four emboli occurred in

49 patients with porcine prosthesis. Twenty-three embolic events occurred in 20 patients with Hancock prostheses (11 undergoing mitral, 8 aortic and 1 mitral plus aortic valve replacement); 31 embolic events occurred in 29 patients with Carpentier-Edwards (16 undergoing mitral, 9 aortic and 4 mitral plus aortic valve replacement). Thirty-eight emboli resulted in residual neurological deficit of which 5 were fatal (Table 4.1).

### **Bleeding**

Bleeding occurred on 52 occasions in 44 patients; on 34 occasions in 28 patients with Bjork-Shiley and on 18 occasions in 15 patients with porcine prostheses, (on 12 occasions in 11 patients with Hancock, and on 6 occasions in 5 patients with Carpentier-Edwards prostheses) (Table 4.1). In five patients bleeding was fatal. Only a small number of episodes of bleeding that had not previously been noted were reported as a result of the questionnaire. The majority of these were minor and did not result in transfusion or hospitalisation. Patients were not taking anticoagulants prior to the episode of bleeding on 4 occasions in patients with the Hancock prosthesis and on two occasions in patients with the Carpentier-Edwards prosthesis. Anticoagulant control was known to be poor prior to 6 episodes of bleeding and was unknown prior to 12 episodes of bleeding. Bleeding was significantly more frequent in those with Bjork-Shiley prostheses.

### **Bacterial Endocarditis**

Bacterial endocarditis occurred on 25 occasions in 19 patients and it occurred twice in six patients.

TABLE 4.1

FATAL AND NON-FATAL EVENTS FOLLOWING VALVE REPLACEMENT

	<u>Numbers of patients (events)</u>			
	Bjork (n=266)	Porcine (n=266)	Hancock (n=107)	Carpentier (n=159)
Emboli	42(59)	49(54)	20(23)	29(31)
Fatal or with residua	17	20	11	9
Bleeding	28(34)	15(18)	10(12)	5(6)
Endocarditis	10(12)	9(13)	2(3)	7(10)
Reoperation	17	53	20	33
Total no Patients	95	126	52	74
Total no Events	120	138	58	80



Endocarditis occurred on 12 occasions in 10 patients with Bjork-Shiley prostheses and on 13 occasions in 9 patients with porcine prostheses, (on 3 occasions in 2 patients with Hancock, and on 10 occasions in 7 patients with Carpentier-Edwards prostheses) Table 4.1. Five patients were successfully treated medically and seven died without reoperation. Seven patients underwent reoperation with one operative death. Only five patients out of the eleven who were successfully treated medically or surgically remain alive.

#### **ACTUARIAL EVENT-FREE SURVIVAL**

Actuarial analysis of event-free survival is presented to the occurrence of first valve-related event (reoperation, embolism, bleeding and bacterial endocarditis) or death.

##### **All patients**

Analysis of actuarial event-free survival for all patients showed a trend towards improved event-free survival with the Bjork-Shiley prosthesis compared with both porcine prostheses grouped together up to 10.0 years of follow-up ( $p = 0.07$ ) and when the Hancock or Carpentier-Edwards prosthesis were considered separately ( $p = 0.15$ ) (Figure 4.1).

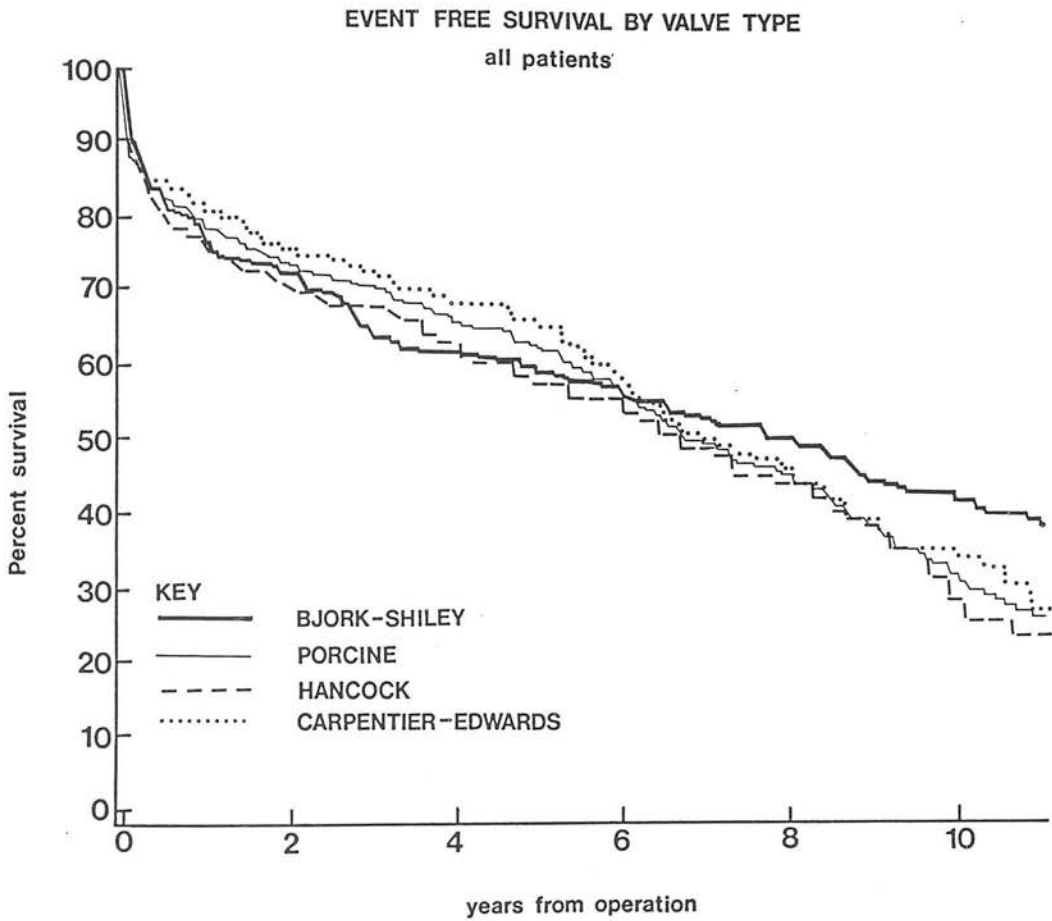
##### **Aortic valve replacement**

Actuarial event-free survival for patients undergoing aortic valve replacement showed no significant difference in event-free survival in those receiving the Bjork-Shiley prosthesis compared with those receiving the Hancock or Carpentier-Edwards prosthesis either when these were

**FIGURE 4.1**

**Edinburgh Heart Valve Study: Results at 10 Years**

All patients undergoing valve replacement: actuarial survival with death or any event (reoperation, bleeding, embolism, endocarditis) as the end point.



considered as a combined group or considered separately (Figure 4.2).

### **Mitral valve replacement**

Actuarial event-free survival for patients undergoing mitral valve replacement showed a non-significant trend towards improved event-free survival for those receiving the Bjork-Shiley prosthesis compared with those receiving the Hancock or Carpentier-Edwards prosthesis when both porcine prostheses were considered as a combined group ( $p = 0.13$ ) and when considered separately ( $p = 0.27$ ) (Figure 4.3).

### **Discussion**

We have not observed a significant difference in event-free survival between patients receiving the Bjork-Shiley mechanical prosthesis and those receiving a bioprosthetic valve. Bleeding occurred more frequently in those receiving the Bjork-Shiley prosthesis as would be expected as all patients with this prosthesis received anticoagulants. This was more than offset however by the significantly increased need for reoperation in those receiving the Hancock and Carpentier-Edwards porcine prostheses as noted in Chapter 3.

The net result was a trend towards improved event-free survival, but this did not reach statistical significance. It is possible that if a larger number of patients had been enrolled in the study this trend would have reached statistical significance. It is also possible that with a more prolonged period of follow up more patients will require reoperation and a significant difference in event-

FIGURE 4.2

Edinburgh Heart Valve Study: Results at 10 Years

Patients undergoing aortic valve replacement: actuarial survival with death or any event as the end point.

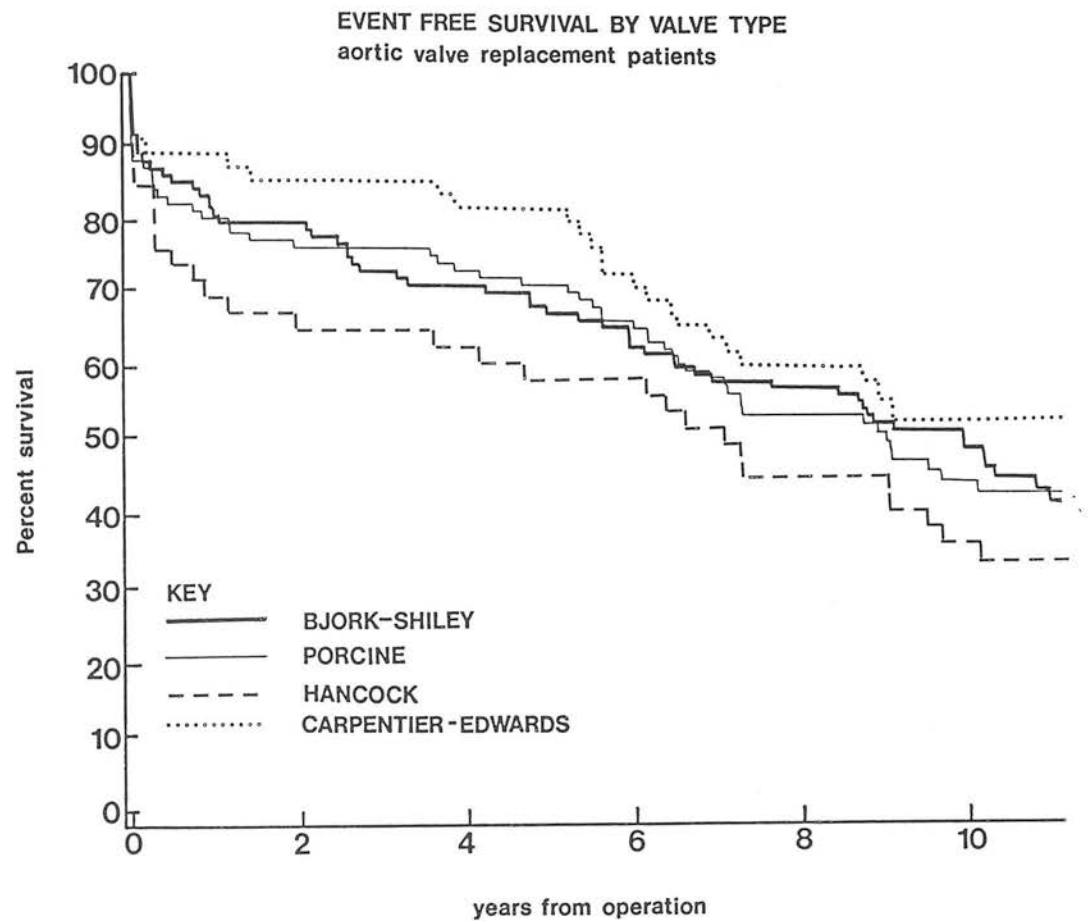
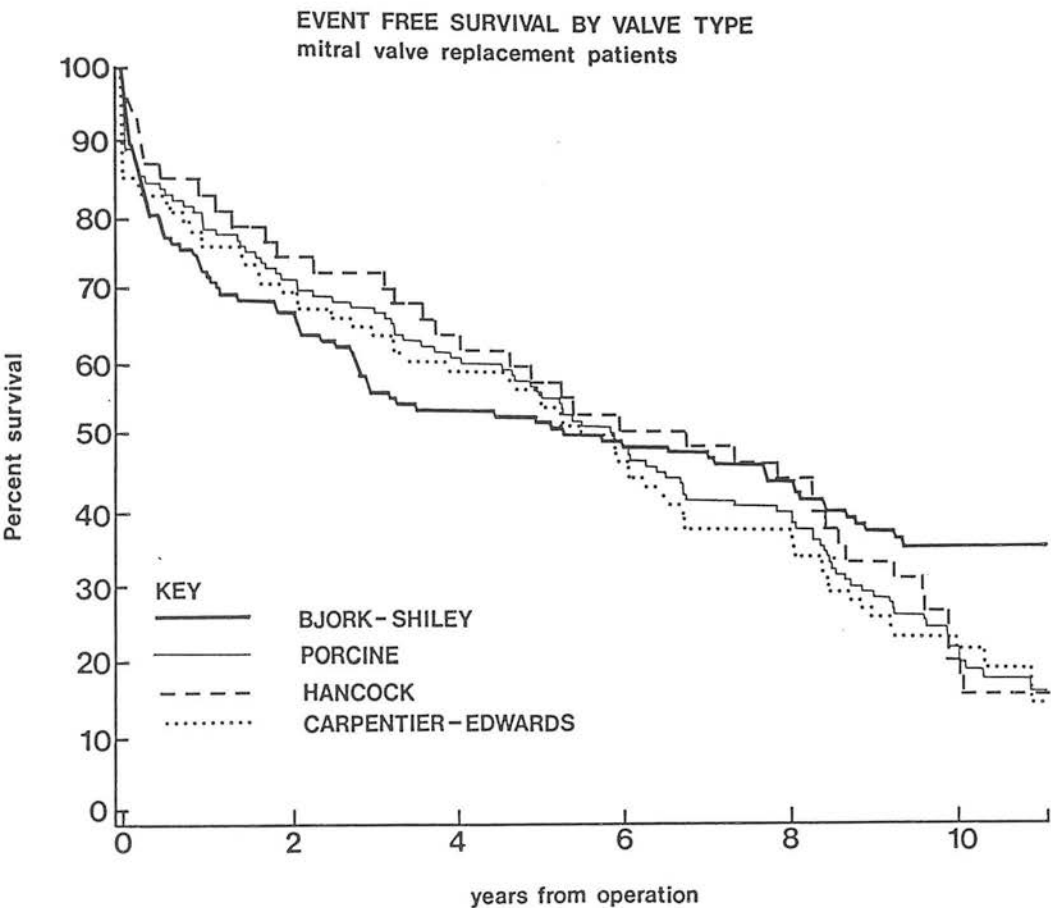


FIGURE 4.3

Edinburgh Heart Valve Study: Results at 10 Years

Patients undergoing mitral valve replacement: actuarial survival with death or any event as the end point.



free survival will develop.

We have made rigorous efforts to record all valve related events and have used a definition of bleeding and embolism similar to those used in the VA study. After a mean follow-up period of 10.5 years how do our results now compare to those of the Veterans Administration Co-operative Study at 5 years? In the V A study 575 patients were entered into a prospectively randomised study comparing the Bjork-Shiley with the Hancock prosthesis in patients undergoing single valve replacement. After a mean of 5 years of follow-up there was no difference in survival between the two groups. There was a significantly greater actuarial freedom from valve-related events in those receiving the Hancock prosthesis whether in the aortic or mitral position. This difference was due to a much higher incidence of bleeding in those receiving the Bjork-Shiley prosthesis; there being no patients requiring reoperation for valve failure due to cusp disruption in those receiving the Hancock prosthesis. In the VA study 209 episodes of bleeding were recorded in 575 patients followed-up for a mean of 5 years. By contrast our study recorded only 59 episodes of bleeding in 532 patients followed-up for a mean of 10.5 years. There are several possible explanations for these differences.

Firstly the definition of bleeding in the VA study required this to be severe enough to lead to hospitalisation or blood transfusion, as in the Edinburgh study. The VA study also included blood transfusion during elective surgery which inevitably led to the recording of

more episodes of 'bleeding'.

Secondly, the differences could have occurred due to differences in the populations study. The patients in the VA study were exclusively male and many required prostatectomy and associated transfusion. The population in the VA study may also have been less meticulous about their anticoagulant control.

Thirdly the proportion of patients with porcine prostheses who were prescribed anticoagulants could have differed. The proportion of patients with bioprostheses in the VA study who received anticoagulants is not stated, but in our study the total number of patient years on anticoagulants was 327 with 1341 patient years on no anticoagulants. It is possible that a higher proportion of patients in the VA study received anticoagulants.

Fourthly the degree of anticoagulation between the two studies was different as previously discussed in Chapter 2. We used a prothrombin ratio of 2.0 - 4.0 which is equivalent to a prothrombin ratio of 1.3 to 2.0 with commercially available reagents used in the USA. A prothrombin ratio of 2.0 - 2.5 used in the VA study would be considered excessive in the United Kingdom and this could further explain the differences in the rates of significant bleeding reported in the two studies. Indeed, latterly in the VA study the recommended prothrombin ratio was reduced to 1.5 to 2.0 for these reasons.

In the light of the results reported in Chapter 3 and above what recommendations can be made for the selection of type of prosthesis for patients requiring valve

replacement? This data analysis suggests that patients who because of atrial fibrillation or for other reasons would normally continue anticoagulants after valve replacement should receive a mechanical prosthesis. In our practice this would include the majority of patients undergoing replacement of the mitral valve. Such patients should have warfarin controlled at a prothrombin ratio of 2.0 - 4.0 which is equivalent to a ratio of 1.3 - 2.0 in the USA.

There is no apparent clear advantage for the use of a mechanical prosthesis in those undergoing aortic valve replacement, but younger patients could benefit from a mechanical prosthesis of proven mechanical durability. Patients in whom anticoagulants must be avoided could receive a bioprosthesis although this might necessitate further operation at a later date.



## CHAPTER 5

### **NON-INVASIVE METHODS OF ASSESSING NATIVE STENOTIC VALVES**

Methods for non-invasive assessment of prosthetic valves have been derived from methods for assessing the function of native and diseased valves. As all prosthetic valves, however well designed, are intrinsically stenotic, the non-invasive methods of assessment of stenotic lesions of native aortic and mitral valves are reviewed in this Chapter. The single most accurate non-invasive method currently available are Doppler ultrasound techniques and these are covered in some greater detail in the latter part of the Chapter and in Chapter 6.

As with all medical investigations, non-invasive physical measurements are complementary to and must be used in conjunction with clinical evaluations; the clinical observations most relevant to the assessment of stenosis are identified below.

#### **Systolic Time Intervals**

The most important physical signs in determining the severity of aortic stenosis are a delayed rise and increased duration of the carotid upstroke, a late peak to the systolic murmur, and a softness of the second heart sound. These characteristics have also been used in the quantitative measurements from phonocardiographic recording of the murmur and analysis of the carotid pulse trace. Thus Voelkel et al (1980) found that the time between the onset of electrical activity of the QRS complex of the electrocardiogram and the peak intensity of the aortic systolic murmur (the Q to murmur peak) was increasingly



prolonged in patients with increasingly severe aortic stenosis. The pre-ejection period (PEP) i.e. the time from the inscription of the QRS complex to initial upstroke of the carotid pulse, and the left ventricular ejection time (LVET) i.e. the time taken for mechanical systole, also alter in aortic stenosis. The ratio of PEP/LVET falls in severe aortic stenosis. Voelkel et al found that systolic time intervals and phonocardiography could separate most patients into those with or without severe aortic stenosis, but they could not quantify the severity more accurately.

In left ventricular failure, the LVET falls and in patients with very severe aortic stenosis and consequent impairment of left ventricular function, the assessment of the severity of aortic stenosis from systolic time intervals is unreliable (Gardin et al 1980). In patients with mitral stenosis analysis of the apex cardiogram has been used to estimate the rate of left ventricular filling in early diastole, which is diminished in mitral stenosis. Phonocardiography can be used to measure the interval between aortic valve closure and mitral valve opening which is reduced in mitral stenosis. Both methods are of limited accuracy and now only of historical interest (Bloomfield et al 1985).

### **Electrocardiography**

The electrocardiogram may accurately detect the presence of left ventricular hypertrophy, which is an almost invariable pathological association with severe aortic stenosis, but the prevalence of co-existing coronary artery disease and hypertension in adult patients with

aortic stenosis mean that such ECG changes are not specific for the presence of severe aortic stenosis. Plain chest radiography may provide pointers to the presence of both aortic and mitral stenosis, but provides only a rough guide to the severity of the lesion.

### Echocardiography

#### **Aortic Stenosis**

Echocardiography can much more accurately detect and quantify aortic stenosis. Left ventricular wall thickness can be measured directly and as the degree of left ventricular hypertrophy is related to overall wall stress, this can be used to estimate left ventricular systolic pressure by the formula devised by Bennett et al (1975).

Systolic intraventricular pressure (kPa) =

$$30 \times \frac{\text{wall thickness (cm)}}{\text{left ventricular transverse diameter (cm)}}$$

Aortic pressure can be estimated from blood pressure obtained by sphygmomanometer and peak to peak gradient across the aortic valve obtained by subtraction. (The conversion factor from kPa to mmHg is 7.5)

Bennett's formula has proved to be highly accurate in quantitating left ventricular pressure, and thus the severity of aortic stenosis in children, but in adult patients in whom hypertrophy can develop with associated conditions the correlation is poorer. Similarly in children and young adults, direct visualisation of the aortic valve by two dimensional echocardiography can determine whether the valve has a normal configuration with three cusps, or is abnormal with two, or even one cusp.

Congenitally stenotic aortic valves tend to be fused at the commissures of the cusps and to form a dome-shape in systole. Only by imaging the whole of the valve cusps by two dimensional echocardiography can the size of the true orifice be determined. Weyman et al (1977) have shown that the maximum separation of the tips of the aortic valve cusps can accurately determine the size of the aortic orifice as determined by cardiac catheterisation. M mode echocardiography which can determine only one single dimension of the valve may be highly inaccurate as the separation of the cusps imaged by the single ultrasound beam may be taken at the base of the leaflets, leading to an erroneously large estimation of the aortic valve orifice.

In adult patients direct visualisation of the aortic valve leaflets produces much less accurate results because fibrosis and calcification of the aortic valve leaflets leads to greatly enhanced ultrasound reflectance and consequent reverberation of the ultrasound signal, which makes the measurement of the separation of two points, that is the valve cusps much less accurate. De Maria et al (1980) found that two dimensional echocardiography was a very sensitive method of detecting valvular aortic stenosis. All of their patients with severe aortic stenosis had a cusp separation of 11 mm or less and 92% of them had a cusp separation of 8 mm or less. The specificity of these values for identifying patients with moderately severe stenosis was, however, poor and 65% of patients with moderately severe aortic stenosis had a cusp

separation of greater than 8 mm. Similar results have been reported by others (Godley et al 1981).

### **Mitral Stenosis**

M mode echocardiography has been used to quantify the severity of mitral stenosis from direct measurements of the mitral valve (Segal et al 1966, Shiu 1977) and by measurements of the rate of left atrial emptying (Strunk et al 1977), and left ventricular filling (Hall et al 1979), both of which are affected by stenosis of the mitral valve. Direct measurement of the mitral valve orifice by two dimensional echocardiography has been shown to be a highly accurate measure of mitral valve area when correlated with measurements made at cardiac catheterisation, and direct measurements made at the time of surgery (Henry et al 1975, Nichol et al 1977).

### **Ultrasound Assessment of Stenotic Valves using the Doppler Principle**

The Doppler technique uses the principle that the velocity of an object moving away from an observer (or receiver) can be determined by the change in frequency of waves of known frequency transmitted from, or reflected from the moving object. Doppler's principle was initially used to determine the speed with which stars were moving away from, or towards Earth by the colour of the light they transmitted to Earth. The principle is equally applicable to ultrasound and the velocity of blood can be determined by the change in frequency of ultrasound waves reflected from the blood corpuscles according to the equation.

$$V = \frac{C \times F}{2 \text{ (transmitted frequency)} \times \cosine \text{ of intercept angle}}$$

where V is blood velocity of blood cells, C is the speed of ultrasound through the body, F is the change in frequency of transmitted ultrasound. The cosine of 0° is 1 and that of 180° is -1 and therefore to minimise the effect of small changes in the angle of the ultrasound beam on measurement of blood velocity, this angle should be kept as close as possible to 0°. Within 20° degrees of 0°, the magnitude of of measured velocity will be reduced by only 6%, but as the intercept angle becomes larger than 20°, the magnitude of the recorded velocity drops sharply and is more sensitive to changes in angle.

#### Measurement of Pressure Drop Across a Stenotic Valve

The Bernoulli equation can be used to describe the pressure drop (P<sub>1</sub>-P<sub>2</sub>) across a stenotic valve.

$$P_1 - P_2 = 1/2p (V_2^2 - V_1^2) + \int_1^2 dv/dt \times ds + R(v)^5$$

where p expresses mass density of a fluid, V<sub>2</sub> = peak Doppler velocity beyond the stenosis, V<sub>1</sub> = peak Doppler velocity proximal to the obstruction, dv/dt x ds = change in velocity/change in time x change in distance, R(v) = viscous resistance of the vessel x local velocity. Combining p for blood with factors that convert gradient to mmHg and velocity to m/s, the coefficient for blood is 3.98 which is usually rounded to 4.0. The second term of the equation (flow acceleration) applies during valve opening and closing when the gradient measurement is not clinically relevant. The third term (viscous friction) has been shown to be unimportant in vitro and in vivo and the

equation can thus be conveniently shortened to  $P_1 - P_2 = 4 (V_2^2 - V_1^2)$

Recent work with sophisticated in vitro experiments have investigated the validity of the modified Bernoulli equation. Redquarth et al (1984) and Holen et al (1985) have compared pressure gradient measured in vitro models that had fluid containing particulate matter passing through a chamber that allowed placement of interchangeable orifices. Correlation between Doppler calculated pressure drop, using the modified Bernoulli equation, and that measured directly was very good.

Usually maximal velocity proximal to a stenotic orifice is less than 1 m/sec and can be ignored without loss of accuracy of the assessment; this further shortens the equation considerably to:

$$P_1 - P_2 = 4 V_2^2$$

The simplicity of the modified Bernoulli equation and the accuracy with which it can be applied to blood flow across a stenotic orifice have led to its widespread use in clinical cardiology. The application of this principle has been facilitated by the development of fast Fourier transformation of the Doppler signal so that a spectral analysis of the signal can be displayed and in this way the highest velocities more easily identified. The method has proved more accurate than the use of a maximal frequency estimator when measuring high velocities. This is important in aortic stenosis in which very high velocities occur and in which the signal to noise ratio may be lowest at the highest velocities, those which are most important



for calculation of the gradient across the valve.

### Measured Doppler Pressure Gradients and their Comparison with those Derived at Cardiac Catheterisation

Holen et al (1976, 1979) applied the modified Bernoulli equation in measuring transvalvular pressure gradient in patients with mitral stenosis. They showed good correlation in mean pressure gradient measured simultaneously by both cardiac catheterisation and the Doppler method. The gradient determined by the modified Bernoulli equation is an instantaneous measurement and has no direct equivalent to measurements made at cardiac catheterisation. There is an inherent delay in peak aortic pressure which occurs after peak left ventricular pressure, even when the two are measured simultaneously by two separate catheters in the left ventricle and aorta. Folland et al (1984) have shown that this is accentuated if peripheral artery pressure is used to substitute for central aortic pressure. The peak pressure gradient calculated from the Doppler velocity profile is the peak instantaneous pressure gradient which has not been used in the assessment of aortic stenosis by cardiac catheterisation. The peak left ventricular to peak aortic pressure is easily measured at catheterisation and most commonly used in clinical practice, but there is no direct equivalent measurement which can be derived from Doppler velocity profiles. Furthermore, the peak aortic pressure in elderly patients, with severely stenotic valves may be high because of lack of compliance in the aorta and arterial tree. It is the mean pressure difference



throughout systole which most accurately reflects the true degree of obstruction to ejection of blood from the left ventricle in aortic stenosis. This is derived from measuring the area between simultaneously obtained (or less accurately superimposed) left ventricular and aortic pressure traces divided by the duration of systole. The only measurement made at cardiac catheterisation and by Doppler ultrasound which is directly comparable is mean pressure gradient (Allen et al 1988).

It has been suggested that this mean pressure gradient can be obtained from the Doppler velocity profile by measuring its area and dividing by its duration to obtain mean velocity, and using the modified Bernoulli equation to calculate mean pressure gradient. In the modified Bernoulli equation, however, there is a squared relationship between velocity and pressure at any one instant, and the true mean pressure gradient should be calculated from the sum of an infinite number of instantaneous measurements along the Doppler velocity profile. In practice this can be approached by calculating instantaneous pressure at 10 msec intervals and averaging these to derive mean pressure thus

$$P = 4[ (V_1)^2 + (V_2)^2 + (V_3)^2 + (V_n)^2 ]$$

Where  $V_1$  = velocity at 10 msec,  $V_2$  = velocity at 20 msec etc.

Manual calculation of this formula is impractical and to be applicable in clinical use the calculation is done by computer.

In many of the earlier papers evaluating the use of

Doppler ultrasound in the assessment of aortic stenosis, comparison was made between the peak instantaneous pressure gradient derived from Doppler measurements, and the peak to peak gradient obtained at catheterisation. Hatle et al (1980), Stamm and Martin (1983), Berger et al (1984) and Simpson et al (1985) in small series of patients all showed a reasonably good correlation between these measurements. It was observed by others that there was frequently "over-estimation" of the peak instantaneous pressure gradient measured by the Doppler technique and peak to peak pressure gradient measured at catheterisation (Kratchek et al 1985). Hegrenaes and Hatle (1985) subsequently also reported that in a larger series of patients with aortic stenosis the peak instantaneous pressure gradient measured by Doppler was consistently higher than the peak to peak pressure gradient measured at cardiac catheterisation. The mean pressure gradient derived from the Doppler measurements by using the integrated equation above correlated very closely with mean pressure gradient measured at catheterisation.

Currie et al (1985) reported a series of 100 consecutive patients with aortic stenosis at the Mayo Clinic who underwent trans-septal catheterisation with direct measurement of left ventricular pressure and aortic pressure and simultaneous continuous wave Doppler measurement of aortic blood velocities. They found a very close correlation between mean pressure gradient measured by the two techniques. They also observed that in comparing peak instantaneous pressure gradient measured by Doppler with peak to peak pressure gradient at

catheterisation the greatest disparity occurred at the lowest mean pressure gradients. In practical terms this could lead to patients with mild aortic stenosis being diagnosed as having a more severe lesion if the Doppler derived data were only loosely interpreted (Yeager et al 1988). It might also be expected to lead to difficulties in accurately measuring the small gradients that typically occur with prosthetic valves.

Thus it has been shown in a number of well conducted studies that measurement of aortic blood velocities in aortic stenosis can provide data about the pressure difference as accurately as that obtained by the most precise (and most invasive) cardiac catheterisation methods.

The measurement of gradient alone however, is not enough to quantify the degree to which the valve is stenosed i.e. the reduction in valve area as the gradient for any specific valve area must obviously be dependent on the flow across the valve, the cardiac output.

#### **Assessment of Valve Area using Doppler Measurement**

Three approaches have been used to calculate valve area from Doppler derived data by making some estimate of cardiac output. The time required for the left atrioventricular pressure gradient to decrease to half of its maximal early diastolic value, the pressure half-time was originally used with catheterisation data. Libanoff and Rodbard (1968) noted that the pressure half-time could be used as an estimate of mitral valve area and was relatively independent of changes in cardiac output, heart rate or the

degree of regurgitation. Hatle et al (1979) derived the pressure half-time from Doppler measurement of transmitral blood flow. Using the modified Bernoulli equation ( $P = 4V^2$ ) they defined the Doppler half-time as the time for transmitral velocity to fall from its peak by a factor of the square root of 2. Hatle and Angelsen subsequently related mitral valve area to Doppler half-time using an empirical constant:

$$\text{Mitral valve area (cm}^2\text{)} = 220 / \text{pressure half-time (msec)}$$

Stamm and Martin (1983) confirmed the validity of this method in a series of 30 patients. Bryg et al (1986) found that, apart from slight discordance between mitral valve area measured by this Doppler technique and by cardiac catheterisation depending on whether the patient was in sinus rhythm or atrial fibrillation there was good correlation between the two measurements. Smith et al (1986) found that mitral valve area measured by Doppler method correlated well with catheterisation data for patients with unoperated mitral stenosis, but less well for those who had previously undergone mitral valvotomy.

Warth et al (1984) obtained cardiac output invasively using a thermodilution Swan Ganz catheter, mean aortic valve gradient obtained by Doppler and calculated valve area from the Gorlin formula. They compared results obtained in this way with those at cardiac catheterisation and found an excellent correlation. Cardiac output can also be measured by Doppler methods combined with two dimensional echocardiography. The amount of blood ejected from the heart with each beat, the stroke volume can be

calculated by multiplying the cross-sectional diameter of the aorta by the time velocity integral of blood velocities obtained from this area by pulsed Doppler measurements. A good correlation has been shown by several investigators between calculations of cardiac output made from measurements derived from the pulmonary artery or aorta, and those made by invasive means (Magnin et al 1981 and Goldberg et al 1982). Such measurements are particularly useful for recording a change in cardiac output in the same patient as the cross-sectional area of the aorta or pulmonary artery remains the same. This method is not as accurate for the absolute measurement of cardiac output, mainly because of errors in the measurement of aortic or pulmonary cross-sectional area. Furthermore, abnormalities of the aortic valve may invalidate such measurements based on the size of the aortic root.

The second approach to measuring effective area of the mitral and aortic valves which has recently been described uses the continuity equation. This states simply that laminar flow through a conduit is equal to the mean velocity times the cross-sectional area of the conduit. With flow remaining constant the ratio of cross-sectional areas at two different sites is inversely proportional to the ratio of the respective mean velocities.

$$Q = A_1 V_1 = A_2 V_2$$

Where  $Q$  is flow,  $A_1$  is the cross sectional area of a normal part of the heart,  $V_1$  is mean velocity through  $A_1$ ,  $A_2$  is the cross-sectional area of the stenosis and  $V_2$  is the mean velocity of blood through  $A_2$ .

If  $A_1$ ,  $V_1$  and  $V_2$  are known then  $A_2$ , the stenotic area, can be derived. In practice  $V_1$  is measured by pulsed wave Doppler in the left ventricular outflow tract and  $A_2$  is the cross-sectional area of the left ventricular outflow tract measured by two dimensional echocardiography. Measurements of aortic valve area by this method were proposed by Zoghbi et al (1986) and have been subsequently validated by Oh et al (1988). The continuity equation has similarly been used for estimation of mitral valve area by Nakatani et al (1988). These methods of assessing the degree of stenosis of a valve by using the continuity equation and Doppler ultrasound techniques are the most accurate non-invasive techniques yet devised.

#### **NON INVASIVE ASSESSMENT OF PROSTHETIC VALVES**

Left ventricular hypertrophy may or may not regress following aortic valve replacement and the measurement of hypertrophy by ECG or echocardiography is unhelpful in assessing the function of aortic valve prostheses. Systolic time interval measurement has not proved useful in assessing prosthetic valves. Evaluation of rigid component prostheses by both M-mode and two dimensional echocardiography is limited because all the components of the prosthetic valve are highly reflective of ultrasound; unless the transducer beam is appropriately directed, the motion of the ball disc or tissue leaflets may be obscured by echoes from these surrounding structures. As an aid to the diagnosis of prosthetic malfunction Brodie et al (1976) used combined phonocardiography and echocardiography to measure the precise intervals between aortic valve closing,

and the mitral valve opening, but this only detected markedly abnormal prosthetic function. The leaflets of porcine prosthetic valves can usually be well imaged by two dimensional echocardiography.

The leaflets may appear thickened with prosthetic stenosis and with infective endocarditis (Alam et al 1979, Shapira et al 1979, Effron and Popp 1983). These findings however are relatively non-specific and may be found with normally functioning older prostheses (Alam et al 1983). Prolapse or rupture of the leaflets of bioprosthetic is often seen with severely regurgitant prostheses (Alam et al 1983, McComb et al 1984). However, two dimensional echocardiography has not facilitated estimation of subtle changes in bioprosthetic valve function.

#### **Doppler Assessment of Prosthetic Valve Function**

In theory the use of the modified Bernoulli equation should also be applicable to the evaluation of prosthetic valves. Flow patterns across prosthetic valves are, however, fundamentally different from those found normally, with further variation between types of prosthesis. Flow through porcine prosthetic valves might be expected to be similar to that through native valves, but flow beyond mechanical valves would be expected to be considerably different with semi-central flow in tilting disc valves and peripheral flow with ball and cage valves.

The modified Bernoulli equation as described above is applicable to flow across prosthetic valves if three conditions are fulfilled.

- (1) Flow must be incompressible, i.e. the density



of blood does not change.

(2) low must be frictionless, i.e. pressure loss due to viscous resistance is negligible.

(3) Flow velocities must be measured along streamlines of the flow.

The first condition can be considered true at pressures found within the heart. With respect to the second condition flow through a prosthetic valve may occur through irregularly shaped orifices, thus creating significant viscous resistance. Thirdly, flow through a prosthetic valve may not be parallel to the streamlines of flow especially for valves with tilting or moving parts.

Yoganathan et al (1978, 1984, 1986) have performed flow visualisation studies of fluid passing through St Jude and Bjork-Shiley mechanical valves and the Carpentier-Edwards porcine valve. They used a laser light source and added tracer particles to the fluid to obtain photographs of flow patterns beyond the prostheses, and showed that with all prostheses flow was principally streamlined. Their studies of porcine valves indicated that their flow stream is indeed central and similar to that through human aortic valves.

Have these theoretical problems interfered with the measurement of pressure gradients across prosthetic valves?

### **In vitro Studies**

Teirstein et al (1985) measured pressure gradients by continuous wave Doppler and by direct manometric measurement across a variety of irregular and multiple stenoses. They used an in vitro model to simulate the left



ventricular outflow tract, and used heparinized blood as the fluid medium. An excellent correlation was found between mean pressure gradient derived by Doppler and manometric methods. Similar results using similar experimental designs have been found by Wong et al (1985) and Redquarth et al (1984).

### **In vivo Studies**

Holen et al (1979, 1981) have demonstrated a very good correlation between mean gradient measured by Doppler and simultaneously recorded by cardiac catheterisation in patients with recently implanted Bjork-Shiley and Hancock valves. Wilkins et al (1986) studied 12 patients with both mechanical and porcine prosthetic mitral or tricuspid valves which were thought to be stenotic. They performed simultaneous continuous wave Doppler and cardiac catheterisation measurements using direct measurement of atrial and ventricular pressure by transseptal catheterisation or direct left ventricular puncture. There was a highly significant correlation ( $r = 0.96$ ) between mean pressure gradient measured by Doppler and manometric methods. The measurement of peak instantaneous pressure gradient by Doppler also correlated well with peak instantaneous pressure gradient measured by simultaneous catheterisation in all three of these studies.

Wilkins et al also compared valve area calculated by cardiac catheterisation using the Gorlin formula to that obtained by the methods described by Hatle (and Angelsen 1982) and Holen et al (1979, 1981). Hatle's method derives valve area by dividing the pressure half-time

derived from the Doppler trace by an empirical constant. Holen's method derives valve area from the cardiac output measured at catheterisation and the velocity of blood flowing across the valve derived from the Doppler tracings. Correlation of prosthetic valve area derived by the Gorlin and Doppler methods was very poor. This might be expected on theoretical grounds because the Gorlin equation assumes a relationship between velocity of blood across a stenotic orifice (which cannot be measured at catheterisation), and the measured pressure difference. The method of Holen measures velocity directly from the Doppler traces. Wilkin's found the correlation between the two Doppler methods was better ( $r = 0.73$ ) than between the Doppler method and catheterisation method.

These results confirm that as in patients both with native stenotic valves and prosthetic valves the measurement of mean pressure gradient across prosthetic valves by Doppler is highly accurate. Measurements of peak instantaneous pressure gradient were also highly accurate and are the easiest measurement to make from the spectral waveform of a Doppler signal. Although this measurement is not used in catheterisation data it is widely used in Doppler analysis. For these reasons I decided to use the measurement of mean pressure gradient and peak instantaneous pressure gradient in comparing the haemodynamic performance of Bjork-Shiley and porcine prosthetic valves implanted a decade previously in the patients enrolled in the Edinburgh heart valve trial. It would be preferable to have some measure of effective valve

area in comparing the performance of these prostheses. The methods based on the continuity equation would not be applicable to all patients enrolled in the valve study as many had disease of native valves or had more than one valve replaced which prevented proper application of the continuity equation. Furthermore, although methods based on the continuity equation had been described they had not been widely validated in 1986 when I commenced this study. At that time the only method which had been widely used and validated was the method of Hatle (1979) using pressure half-time. For this reason I decided to employ this as a measure of effective valve area in patients with mitral valve prostheses; the results of these investigations are presented in the next chapter.

## CHAPTER 6

### COMPARISON USING DOPPLER ECHOCARDIOGRAPHY OF HAEMODYNAMIC PERFORMANCE OF THE BJORK-SHILEY AND PORCINE PROSTHESES ONE DECADE AFTER IMPLANTATION

The haemodynamic performance of Bjork-Shiley and porcine prostheses have not so far been compared several years after implantation. Khuri et al (1988) reported a haemodynamic comparison of the Bjork-Shiley and Hancock prostheses in half of the patients enrolled in the VA Cooperative valve study investigated six months after implantation. They showed a small advantage to the Bjork-Shiley prostheses when used in the aortic position but no difference in the mitral position. Other studies of haemodynamic function had also largely been done shortly after implantation of the prosthesis (Bjork et al 1973, Lurie et al 1977, Cotter and Miller 1979, Thormann et al 1981, Horskotte et al 1983, Gray et al 1984). Lipson et al (1982) have reported a deterioration in haemodynamic performance of porcine prostheses used in the mitral position. Eighteen patients were studied by cardiac catheterisation six months post operatively and at an average of 7 years after surgery. Over this period the average value of mean pressure gradient rose from  $5.9 \pm 0.7$  mmHg to  $8.6 \pm 0.7$  mmHg.

The patients in the Edinburgh valve study provided an excellent opportunity to compare haemodynamic performance of these prostheses 8 - 12 years after implantation and Doppler echocardiography as described in Chapter 5 provided an accurate method of assessing the haemodynamic

performance non-invasively. In consequence, the aim of this study was to measure the haemodynamic performance of Bjork-Shiley and porcine prosthetic valves approximately one decade after implantation and to assess any significant difference in performance occasioned by their use over this period of time.

### **Patients**

All surviving patients enrolled in the Edinburgh heart valve study were considered for Doppler examination. In July 1988 of the 532 randomised patients analysed in the Edinburgh valve trial there were 241 survivors who had not undergone further valve replacement or been lost to follow up. Approximately two thirds of the patients had originally been referred from the Western General Hospital and followed-up by the cardiologists at that hospital or associated peripheral clinics in Stirling, Kirkcaldy and Inverness. Patients had been enrolled in the study from John O'Groats (one patient!) in the north to Whitehaven in Cumbria in the south. Doppler ultrasound equipment is only available at the Royal Infirmary and patients attending for routine review underwent a Doppler examination there, either at a routine clinic visit, or by separate appointment. A total of 52 aortic valve prostheses and 50 mitral valve prostheses were examined in 96 patients. Doppler signals adequate for analysis were recorded across 47 of the aortic prostheses and all of the mitral prostheses. In the majority of patients with mitral prostheses the size of the prosthesis was 33 mm, but a minority of patients had smaller or larger prostheses

(Table 6.1). Prostheses of a variety of sizes had been implanted in patients undergoing aortic valve replacement (Table 6.1), but the distribution of sizes between those with Bjork-Shiley and porcine prostheses was similar.

### **Methods**

All Doppler examinations were performed by either myself or Miss Ann Colthart, chief physiological measurement technician, in a standard manner, with a Hewlett-Packard ultrasonograph model 7700. Doppler examinations performed by other staff were not considered because differences in technique can lead to recording of suboptimal Doppler traces, which although adequate for diagnostic work, would be unsuitable for analysis of small differences of performance of individual valves.

All patients underwent a complete two dimensional echocardiographic examination in the left lateral decubitus position. M-mode recordings of maximal left ventricular dimensions were made from the body of the left ventricle from the parasternal short axis view, and those of the left atrium from the parasternal long axis view. Doppler recordings were made from the apex or left axilla in patients with mitral prostheses. Both pulsed wave and continuous wave Doppler recordings were made with adjustment of transducer position, so that an optimal audio signal including the highest frequencies was obtained.

Patients with mitral valve prostheses were also asked to undergo a treadmill exercise test with full 12 lead monitoring. They were exercised using the Naughton 3 mph test which maintains a constant treadmill speed of 3 mph

TABLE 6.1

NUMBERS OF PATIENTS EXAMINED WITH EACH SIZE OF PROSTHETIC VALVE**AORTIC VALVE REPLACEMENT**

	Bjork-Shiley	Porcine
29 mm	2	1
27 mm	9	3
25 mm	5	7
23 mm	6	10
21 mm	2	2
19 mm	1	0
Not known	<u>0</u>	<u>1</u>
<b>Total</b>	25	22

**MITRAL VALVE REPLACEMENT**

35 mm	0	2
33 mm	29	11
31 mm	<u>5</u>	<u>3</u>
<b>Total</b>	34	16

and increases the slope of the treadmill by 2% every two minutes starting from a baseline of 0%. If patients could not manage a speed of 3 mph this was reduced to 2 mph but the slope increments increased as before. Patients were exercised to limiting symptoms of dyspnoea or fatigue. Immediately on ceasing exercise they were transferred to an examination couch and Doppler recordings repeated as before.

For patients with aortic prostheses only continuous wave recordings were made as aliasing of the signal occurred with pulsed wave Doppler at blood velocities found with these prostheses. The transducer was placed at the apex or left axilla in the left lateral position, at the right sternal edge in the right lateral position, and in the subcostal area, or in the suprasternal notch in the semi-recumbent position in all patients. The transducer was angulated in each position to record the optimal audio signal incorporating the maximal frequencies which could be obtained. These techniques were necessary to ensure that the Doppler ultrasound beam was travelling as close as possible to the direction of blood flow through the prosthetic valve. Recordings were made on the stereophonic audio channels of a Sony Betamax video tape recorder. Spectral analysis of the Doppler signal was recorded simultaneously on the video channel of the video recorder and also on hard copy using the dedicated Honeywell strip chart recorder.

### **Analysis of Doppler Wave Forms**

#### **Audio Signal**

The audio signals were played back through the



spectral analyser of a Doptek continuous wave Doppler ultrasound machine. This system has a 20 second memory and playback loop, with facilities for outlining the spectral wave form using a light pen system interfaced with the TV monitor (Figure 6.1). The wave forms thus outlined can be transferred to a BBC microcomputer for analysis (Figure 6.2). At least 3 consecutive waveforms for patients in sinus rhythm and at least 5 consecutive waveforms for those in atrial fibrillation were analysed. Variation in the intensity of the Doppler signal with respiration occurred in some patients, precluding analysis of this number of consecutive beats. If this problem occurred then a similar number of non-consecutive beats were analysed. If possible all waveforms from the 20 second playback loop were analysed.

#### **Computer Analysis of Audio Waveforms**

Peak velocity of the audiosignal was calculated at 10 msec intervals along the waveform using the Doppler equation as described previously. The point of maximal velocity was identified from the waveform. The upslope of the waveform was calculated as the rate of rise from the initial inscription of the waveform to maximal velocity. The pressure half-time was calculated as the time taken for the velocity of the waveform to fall from its maximal point to the point where velocity was equal to maximal velocity divided by the square root of two. If this velocity was not achieved the downslope was extrapolated to enable calculation of the pressure half-time. Peak instantaneous pressure gradient was calculated from maximal velocity

FIGURE 6.1

Top panel: Doppler signal obtained from a patient with a mitral valve prosthesis. The patient is in sinus rhythm and there are therefore two peaks to the wave form, the first representing pressure filling and the second atrial filling. Lower panel: the same Doppler waveform has been drawn around with the light pen system and is outlined by a faint line.

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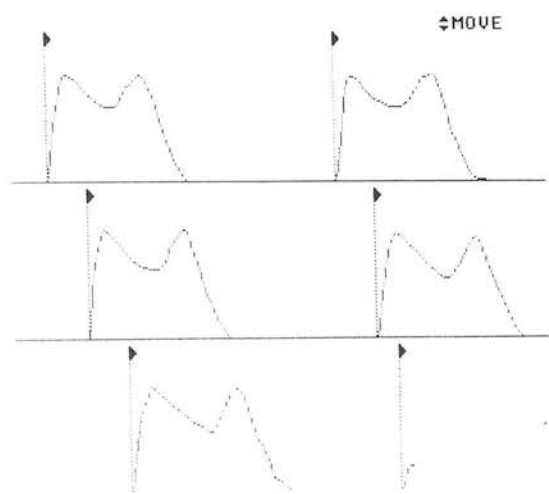
RANGE 4kHz | SWEEP 5ms | ALT |  
ENTERB PRINTB DUMPB EXITB  
P1= 2.79 TAM= 1002 HZ



RANGE 4kHz | SWEEP 5ms | ALT |

**FIGURE 6.2**

The outline of Doppler waveforms from five consecutive beats have been transferred to the BBC computer. The beginning of each waveform is flagged for subsequent quantitative analysis by the computer.



using the modified Bernoulli equation. Mean pressure gradient was calculated as the arithmetic mean of instantaneously derived pressure calculated at 5 msec intervals along the Doppler waveform according to the formula given previously. For purposes of comparison mean gradient was also calculated from the formula:

$$\text{Mean pressure gradient (mmHg)} = 4(\overline{V})^2$$

where  $\overline{V}$  is mean velocity obtained from measurement of the area under the waveform. The values of peak velocity measured in this way (from two sample wave forms) were compared with those calculated from the spectral display of the Hewlett-Packard system recorded on the video channel for simultaneously recorded individual waveforms obtained from each patient.

#### Computer Analysis of Waveforms Recorded on Hard Copy

Peak velocity was derived for all waveforms from hard copy recordings by manual measurement. Similarly, pressure half-time was calculated manually from a selection of waveforms for comparison with those obtained by computer analysis. Computer analysis of waveforms recorded on hard copy was done by two methods. Firstly the hard copy recordings were transferred to a video monitor using a television camera; this permitted some magnification of the wave form to facilitate the tracing of the outline of the waveform. A tracking rollerball was used to move a cursor on the TV monitor around the outline of the waveform, and to highlight the points of calibration for measurement of velocity and the speed at which the copy was recorded. The waveforms were then transferred to a BBC

microcomputer for analysis using the programme as mentioned above.

Secondly a commercially developed computer analysis system was used (Sonotron/Diasonics). This system is designed to facilitate the analysis of hard copy recordings using a magnetic graphics pad and "gunsight mouse" interfaced with an IBM PC microcomputer. The hard copy recordings from the Hewlett Packard strip chart recorder were made on silver-backed paper which interfered with proper functioning of the graphics pad. This problem was overcome by photocopying the original recordings and analysing the photocopied traces. For copyright reasons the programme for this system was not available for detailed inspection. The method quoted for calculation of mean pressure gradient was that of Otto et al (1986) and was similar to that used in our own programme. Results of analysis of the same waveform using both methods were compared and found to be in excellent agreement. This was reassuring but to be certain that no small measured difference in the performance of the different types of prosthesis were due to unrecognised variation in the methods of analysis, the comparison of the different types of prosthesis was made using only the same method of analysis. The method based on the BBC programme was used for comparison of the mitral prostheses and the Sonotron/Diasonics programme are for comparison of aortic prostheses.

### **Statistical Analysis**

The measurements were analysed using "Epistats", a

computer software statistical package designed for analysis of small data sets and suitable for use with the IBM PC microcomputer. The paired and unpaired t test was used to assess the differences in the means of continuous variables for paired and unpaired samples. The Pearson correlation coefficient was calculated for analysis of linear regression.

### **Comparison of Hewlett Packard and Doptek Spectral Analysis of Doppler Signal**

The spectral profiles produced by the spectral analyser of the Hewlett Packard and Doptek machines were compared by recording known velocities in a pump simulator by the method of McDicken (1986). The velocities recorded by each machine were identical across a range of velocities up to a maximal velocity of 2 m/s.

Comparison was made between the maximal recorded velocities estimated by the Doptek spectral analyser from the Doppler signal recorded on the audio channel of the video tape recorder and the simultaneously displayed spectral profile recorded on the video tape recorder. For patients with mitral prostheses the correlation was good. Peak velocity recorded by both systems differed by less than 10%. There was one limitation in that exact measurement of peak velocity was difficult to calculate from the velocity profiles as recorded on the video channel because of the small size of the velocity profile and the limited scale (only 1 m/sec intervals) displayed on the video screen. In all cases the audio Doppler signal was strong and spectral display was clearly defined on both

Hewlett Packard and Doptek systems.

In marked contrast the spectral display of maximal velocities from patients with aortic prostheses was poor with the Doptek spectral analyser when the audio signal was weak. Maximal velocities were poorly defined and an increase in overall gain often led to an increase in noise level and a poor spectral envelope. The strength of the Doppler signal at maximal velocities was usually weaker for aortic prostheses as compared with mitral prostheses. This problem was exacerbated by the recording of the Doppler signal from some patients with aortic prostheses at a low recording level on one of the stereo channels of the video cassette recorder.

For these reasons it was preferred that Doppler spectral velocity signals from patients with aortic prostheses were recorded on hard copy direct from the Hewlett-Packard ultrasound machine and the data then analysed as outlined above; for ease of use I employed the Sonotron/Diasonics analysis system based on the IBM PC computer. Doppler signals obtained from flow across mitral prostheses were analysed with the computer software based on the BBC computer usually from the audio channel recordings and without the need for a hard copy record.

One unsuspected result in the Hewlett-Packard spectral analysis of the Doppler signal was seen in patients with Bjork-Shiley mechanical prostheses where the spectral velocity profile was affected by the "clicks" of the mechanical prosthesis. The Doppler signal was frequently attenuated for up to 50 msec after the "opening click" of

the prosthesis. An example of this phenomenon is shown in Figure 6.3. and it is probably due to the spectral analyser having an automatic gain compensation so that gain is reduced for a period of time following a very strong audiosignal (such as that created by the opening of the prosthetic disc). In practice it had little effect on the delineation of the spectral velocity profile but it proved impossible to identify the upslope (rate of rise) of the signal and therefore the measurement could not be used in any comparative analyses.

## **RESULTS - OBSERVATIONS ON MITRAL VALVE PROSTHESES**

### **Measurements of Left Atrial and Left Ventricular Dimensions by M Mode Echocardiography**

M Mode echocardiographic recordings suitable for analysis were obtained in 45 of 50 patients with mitral prostheses. There was no statistically significant difference in chamber sizes between patients with porcine and those with Bjork-Shiley prostheses (Table 6.2). The mean fractional shortening was  $27\% \pm 9\%$  in those with porcine prostheses and  $31\% \pm 8\%$  in those with Bjork-Shiley prostheses, a difference not statistically significant. Fractional shortening was less than 25% (indicating significant depression of left ventricular function) in 5 patients with porcine prostheses (17%, 19%, 19%, 21% and 22%) and in 4 patients with Bjork-Shiley prostheses (15%, 16%, 23% and 24%).

### **Measurement of Mean Pressure Gradients from Doppler Recordings**

Calculation of mean pressure gradient was done by the



FIGURE 6.3

Doppler signal obtained from a patient with a Bjork-Shiley mitral prosthesis. The part of the Doppler spectral profile following the opening click (OC) of the prosthesis is attenuated by the automatic gain compensation system. The closing click is seen at the end of the Doppler spectral profile.

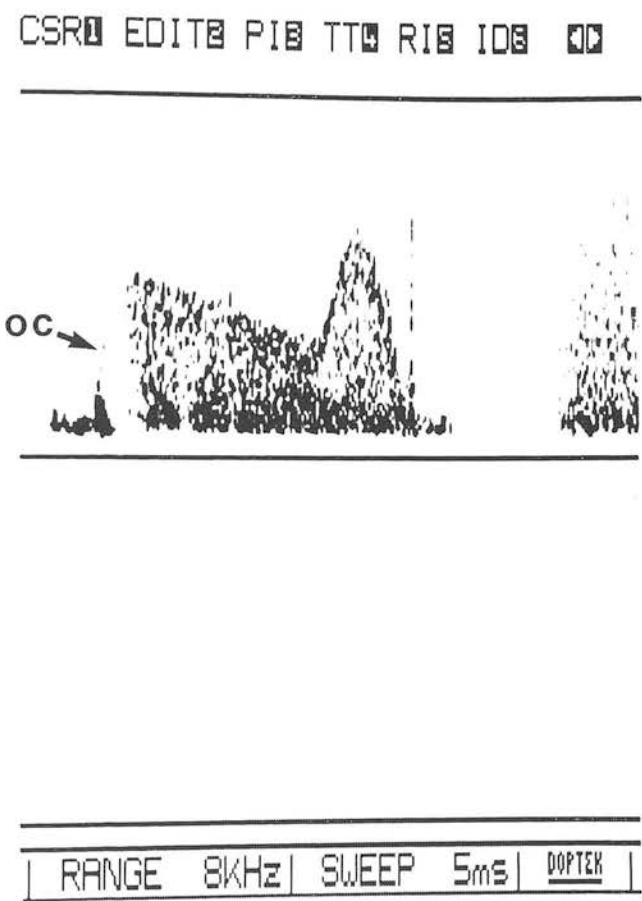


TABLE 6.2

MEAN LEFT ATRIAL AND LEFT VENTRICULAR DIMENSIONS IN PATIENTS WITH  
MITRAL VALVE REPLACEMENT

	Bjork-Shiley	Porcine
Left atrial dimension (mm)		
Mean	54	55
SD	10	9
Left ventricular end- diastolic dimension (mm)		
Mean	50	50
SD	8	8
Left ventricular end- systolic dimension (mm)		
Mean	35	38
SD	8	9
Fractional Shortening		
Mean	31	27
SD	8	9

two methods described previously, by integration of multiple calculations of instantaneous pressure made at 5 msec intervals along the Doppler velocity profile and by calculating the average velocity and from this deriving mean pressure gradient. Mean pressure gradient calculated by integration was, as anticipated, consistently higher than that calculated from average velocity. The mean pressure gradient across porcine mitral prostheses was  $3.4 \pm 1.4$  mmHg calculated by the integration method and  $2.6 \pm 1.2$  mmHg calculated by the method using average velocity. The equation describing the relationship was:

Mean pressure gradient by integration method (mmHg) =  $1.11 \times$  mean pressure gradient from average velocity + 0.45 mmHg

There was a close correlation between the two values ( $r = 0.98$ ).

This relationship is shown in Fig 6.4.

In patients with Bjork-Shiley mitral valve prostheses the mean pressure gradient calculated by the integration method was  $3.0 \pm 1.3$  mmHg, and  $2.4 \pm 1.2$  mmHg calculated by the method using average velocity. The equation describing the relationship was:

Mean pressure gradient by integration method (mmHg) =  $1.04 \times$  mean pressure gradient from average velocity + 0.64 mmHg

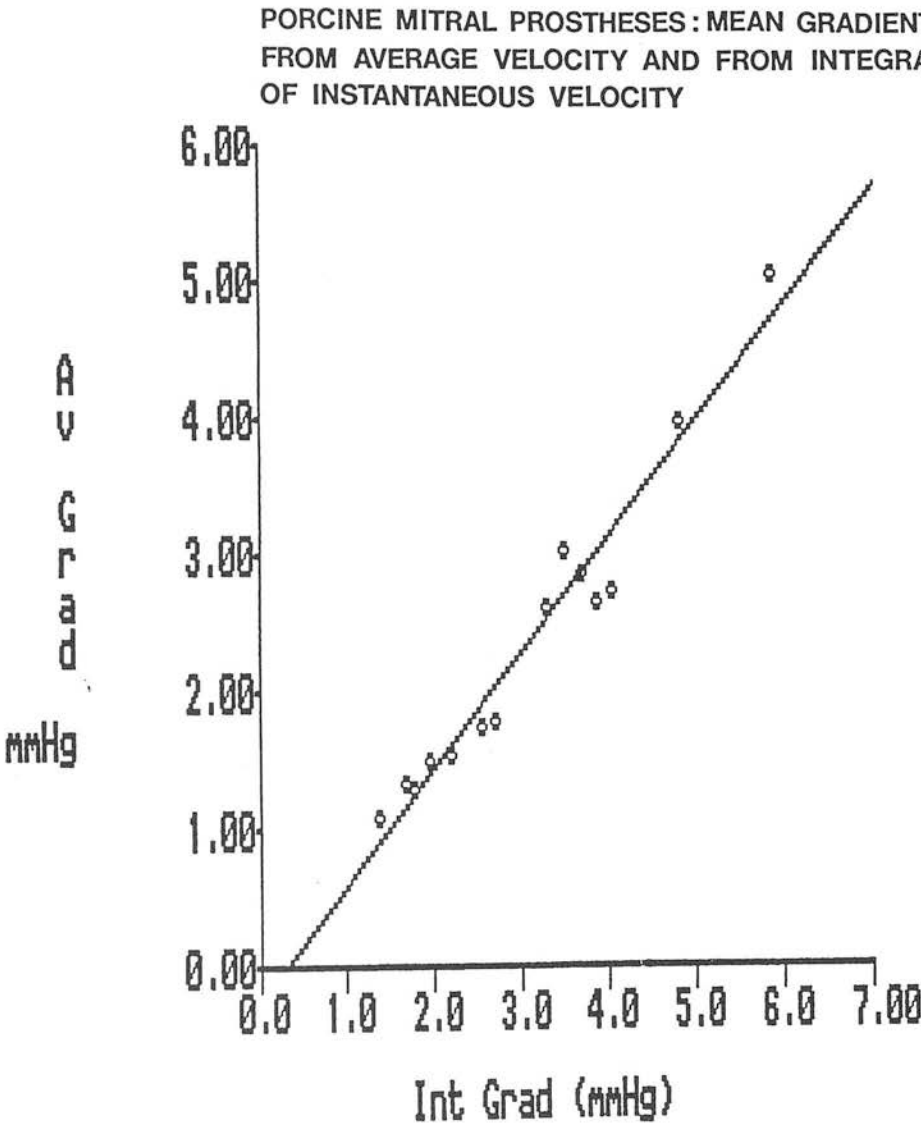
There was a close correlation between the two values ( $r = 0.98$ ).

This relationship is shown in Fig 6.5.

The calculation of mean pressure gradient by the integration method is theoretically more valid and was

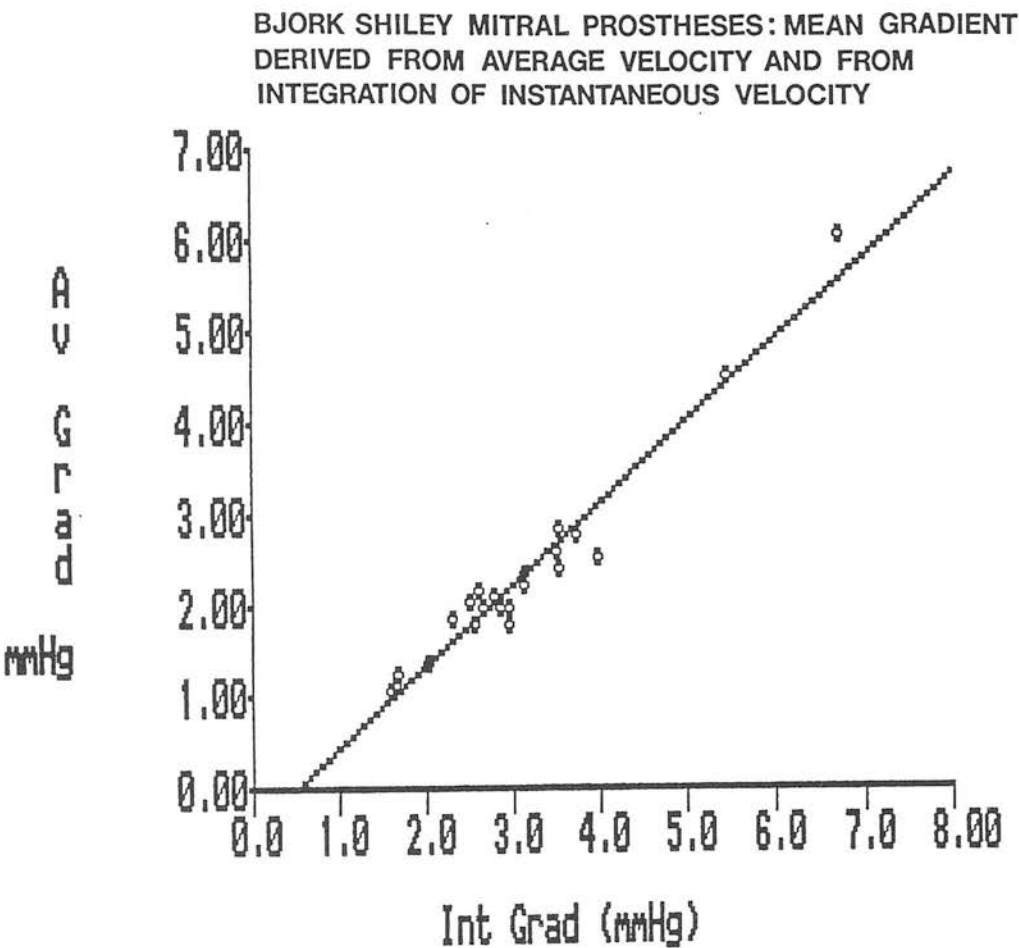
FIGURE 6.4

Comparison of mean pressure gradient in mmHg derived from the average velocity (Av grad), and that derived by integrating the values obtained for instantaneous velocity at 10 msec intervals along the Doppler spectral profile (Int grad) for patients with porcine mitral valve prostheses.



**FIGURE 6.5**

Comparison of mean pressure gradient in mmHg derived from the average velocity (Av grad), and that derived by integrating the values obtained for instantaneous velocity at 10 msec intervals along the Doppler spectral profile (Int grad), for patients with Bjork-Shiley mitral valve prostheses.



consistently higher than that calculated from average velocity. The former calculation of mean pressure gradient has in consequence been used throughout the remainder of this chapter.

### **Comparison of Mean and Peak Instantaneous Pressure Gradients**

There was a weak correlation between mean pressure gradient peak and instantaneous pressure gradient in recordings from patients with porcine and Bjork-Shiley mitral valve replacements. The correlation coefficient for the two measurements for patients with porcine mitral valve replacements was 0.78 and 0.62 for patients with Bjork-Shiley mitral valve replacements.

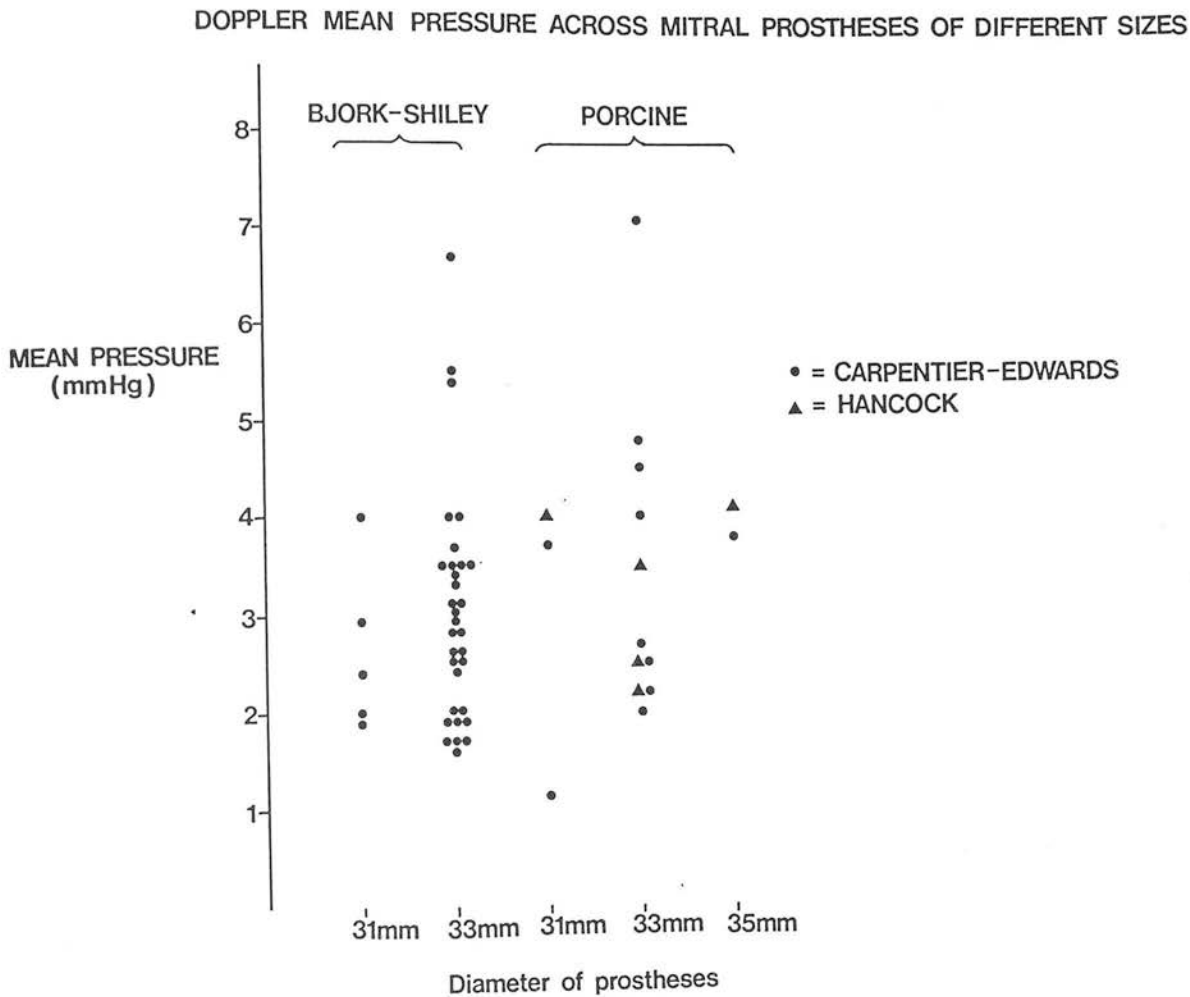
### **Comparison of Pressure Gradients Across Mitral Prostheses of Different Sizes**

There was a wide variation in the mean pressure gradient measured across mitral prostheses of the same size. This is best illustrated by the range of mean pressure gradients measured across the 33 mm Bjork-Shiley prosthesis. There were 29 patients with this size of prosthesis, the largest single group of patients with one size of prosthesis incorporated in this study. The lowest mean pressure gradient was 1.57 mmHg and the highest 6.70 mmHg in the group. Mean pressure gradients for prostheses of different sizes are depicted in Figure 6.6. There was overlap of values between the groups and for purposes of comparison of the prostheses these groups were amalgamated.

There was similarly a wide variation in peak instantaneous pressure gradient measured across mitral

FIGURE 6.6

Mean pressure gradient measured at rest across Bjork-Shiley and porcine mitral valve prostheses of different sizes.



prostheses of the same size with considerable overlap between groups.

#### **Comparison of Pressure Gradient across Bjork-Shiley and Porcine Mitral Prostheses**

The mean pressure gradient for all patients with Bjork-Shiley prostheses was  $3.0 \pm 1.2$  mmHg and was  $3.4 \pm 1.4$  mmHg for patients with porcine prostheses (Figure 6.7).

The mean peak instantaneous pressure gradient for patients with Bjork-Shiley mitral prostheses was  $9.0 \pm 2.4$  mmHg and  $8.9 \pm 3.2$  mmHg for those with porcine mitral prostheses. These values were not significantly different (Figure 6.8).

#### **Comparison of Pressure Half-Time of Bjork-Shiley and Porcine Mitral Prostheses**

There was a large range of pressure half-time measurements in patients with prostheses of the same size illustrated by the range for 33 mm Bjork-Shiley mitral prostheses which varied from 67 to 182 msec (Fig 6.9). There was considerable overlap between prostheses of different sizes (Fig 6.9). When all Bjork-Shiley prostheses were considered together mean pressure half-time was  $87 \pm 28$  msec compared to  $114 \pm 36$  msec for porcine mitral prostheses, a difference which was statistically significant ( $p = 0.05$ ) (Figure 6.10).

#### **Results of exercise studies**

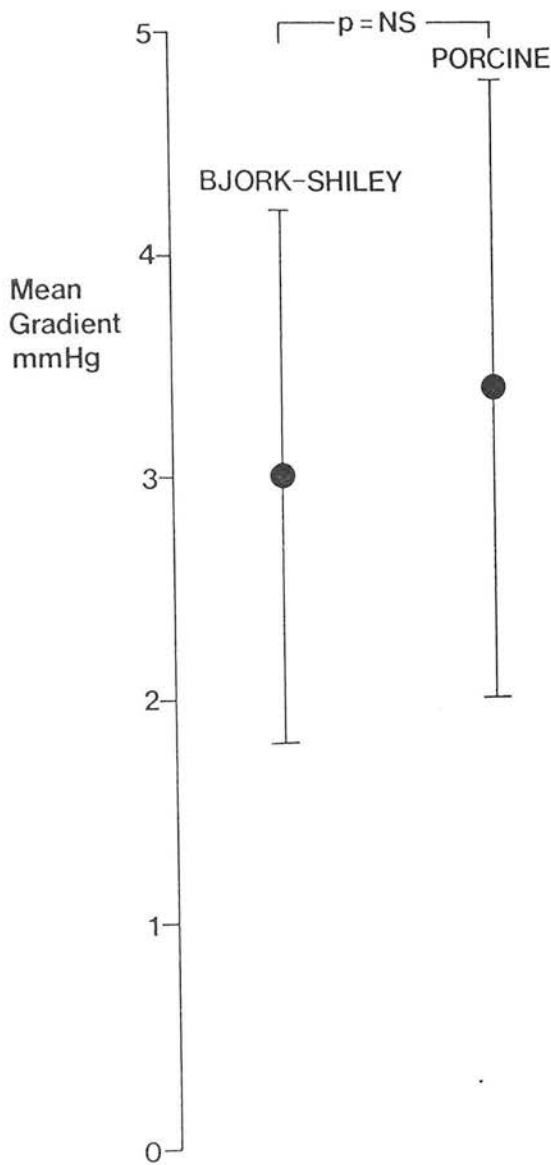
Seventeen patients with Bjork-Shiley and eight patients with porcine prostheses successfully completed an exercise test with adequate recordings of the mitral Doppler signal made after exercise. In two patients with



**FIGURE 6.7**

Mean values ( $\pm$ SD) of mean pressure gradient at rest across Bjork-Shiley and porcine mitral valve prostheses.

MEAN GRADIENT ACROSS MITRAL PROSTHESES (MEAN  $\pm$  SD)



**FIGURE 6.8**

Mean values ( $\pm$ SD) of peak instantaneous pressure gradient at rest across Bjork-Shiley and porcine mitral valve prostheses.

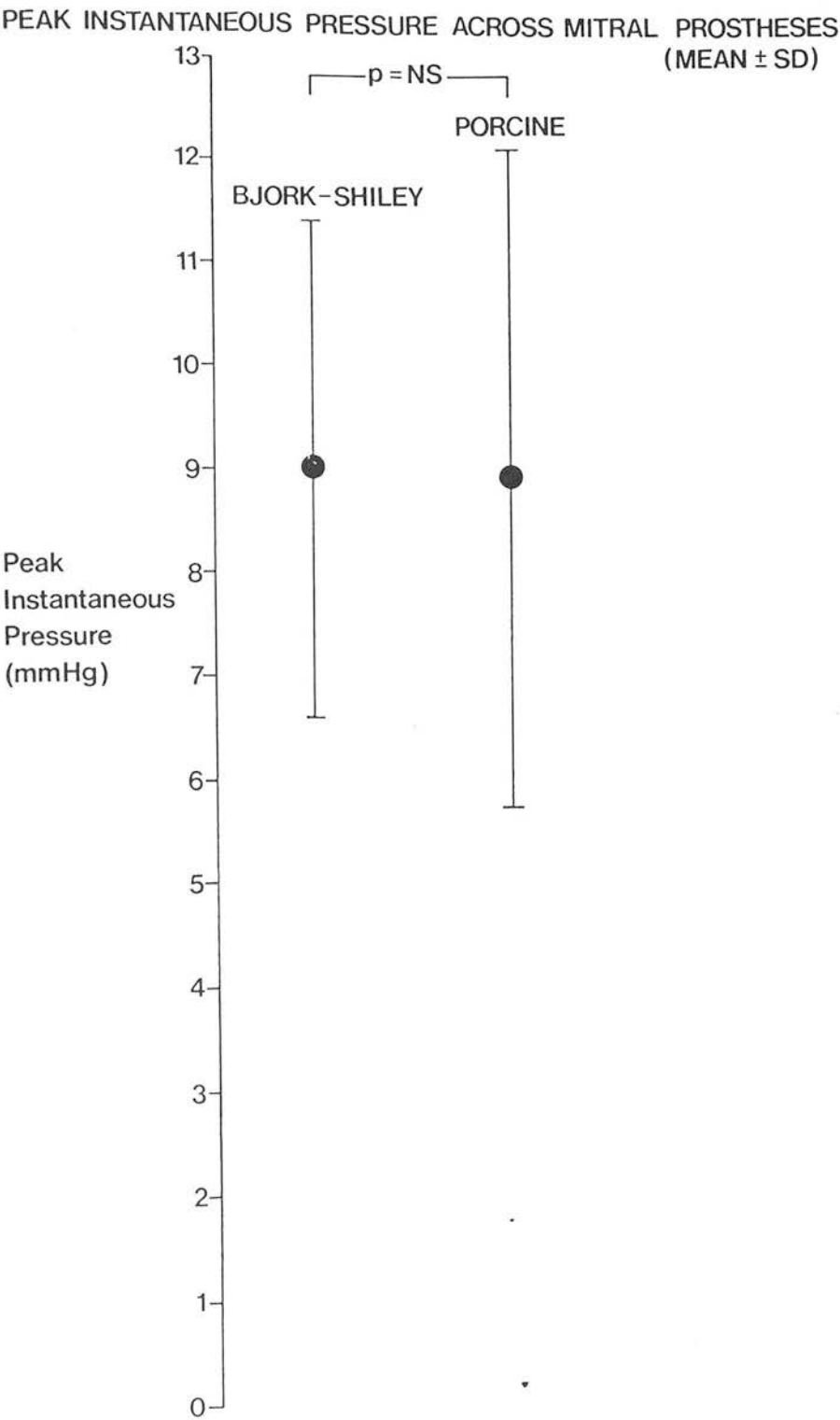


FIGURE 6.9

Pressure half-time measured at rest across Bjork-Shiley and porcine mitral valve prostheses of different sizes.

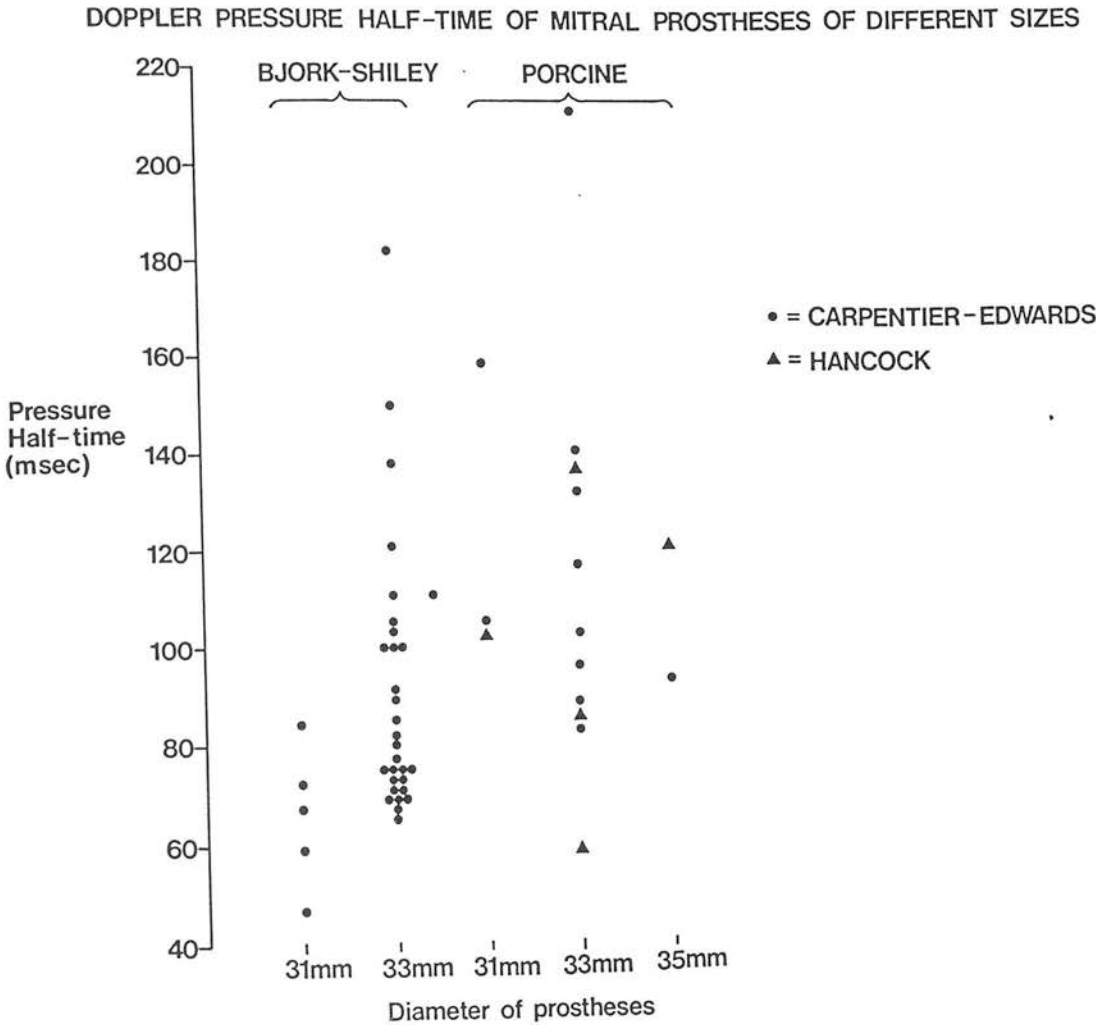
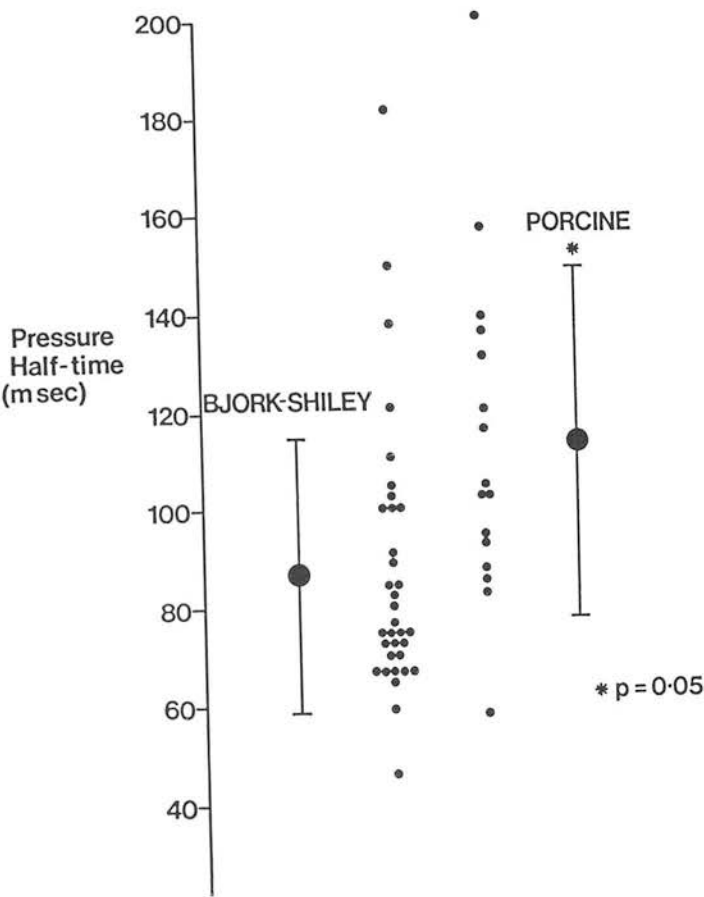


FIGURE 6.10

Mean values ( $\pm$ SD) of pressure half-time at rest across Bjork-Shiley and porcine mitral valve prostheses.

DOPPLER PRESSURE HALF-TIME OF BJORK-SHILEY AND PORCINE MITRAL PROSTHESES



the Bjork-Shiley prostheses and one with a porcine prosthesis a Doppler signal adequate for quantitative analysis could not be recorded after exercise. Three patients could not manage to exercise on the treadmill and the remainder did not wish to attempt treadmill exercise.

#### **Effect of Exercise on Mean Gradient across Mitral Prostheses**

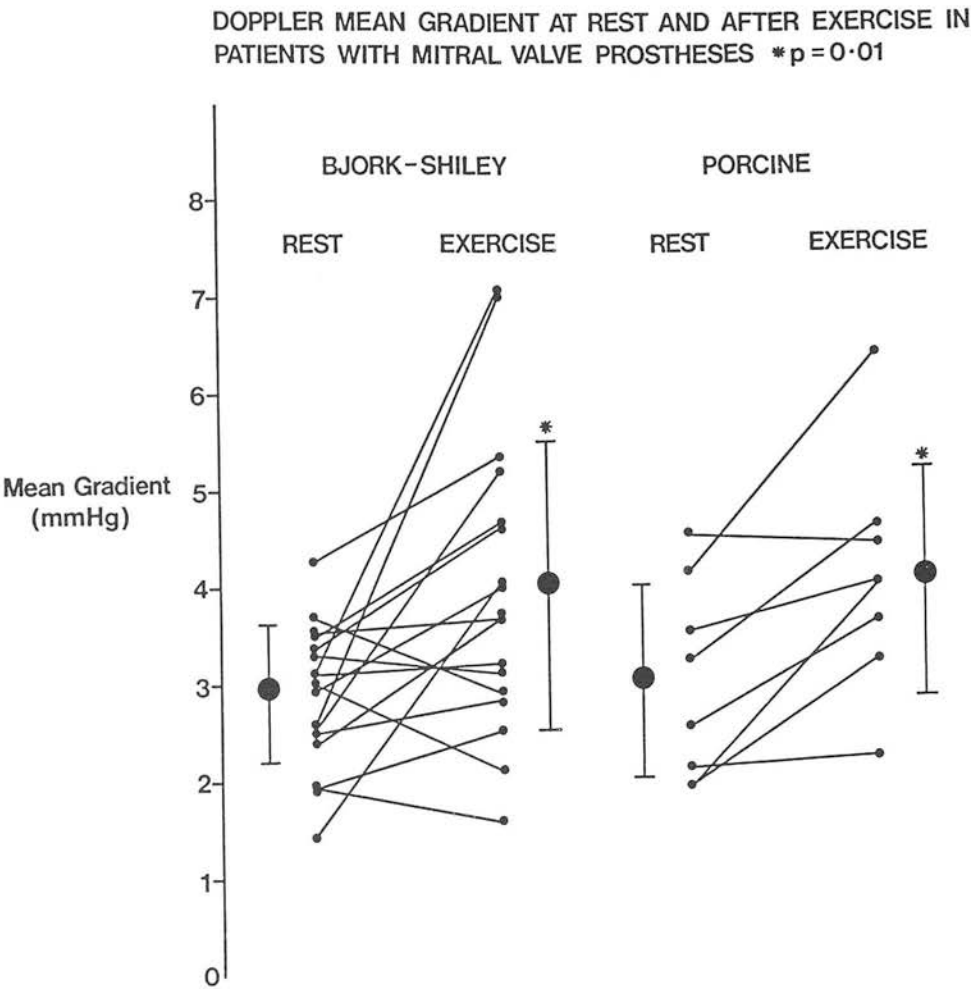
The mean of the mean pressure gradient for those patients with Bjork-Shiley prostheses who successfully completed an exercise test was  $2.9 \pm 0.7$  mmHg at rest and increased significantly ( $p = 0.01$ ) to  $4.0 \pm 1.5$  mmHg immediately after exercise (Fig 6.11). The mean of mean pressure gradient for those patients with a porcine mitral prosthesis was  $3.0 \pm 1.0$  mmHg at rest and increased significantly ( $p = 0.01$ ) to  $4.1 \pm 1.5$  mmHg immediately after exercise (Fig 6.11).

#### **Effect of Exercise on Pressure Half-time of Mitral Prostheses**

The mean of pressure half-time for patients with Bjork-Shiley mitral prostheses who successfully completed an exercise test was  $98 \pm 28$  msec at rest and was not significantly different at  $91 \pm 30$  msec immediately after exercise (Fig 6.12). The mean of pressure half-time for patients with porcine mitral prostheses was  $127 \pm 27$  msec at rest and fell significantly ( $p = 0.05$ ) immediately after exercise to  $97 \pm 22$  msec (Fig 6.12).

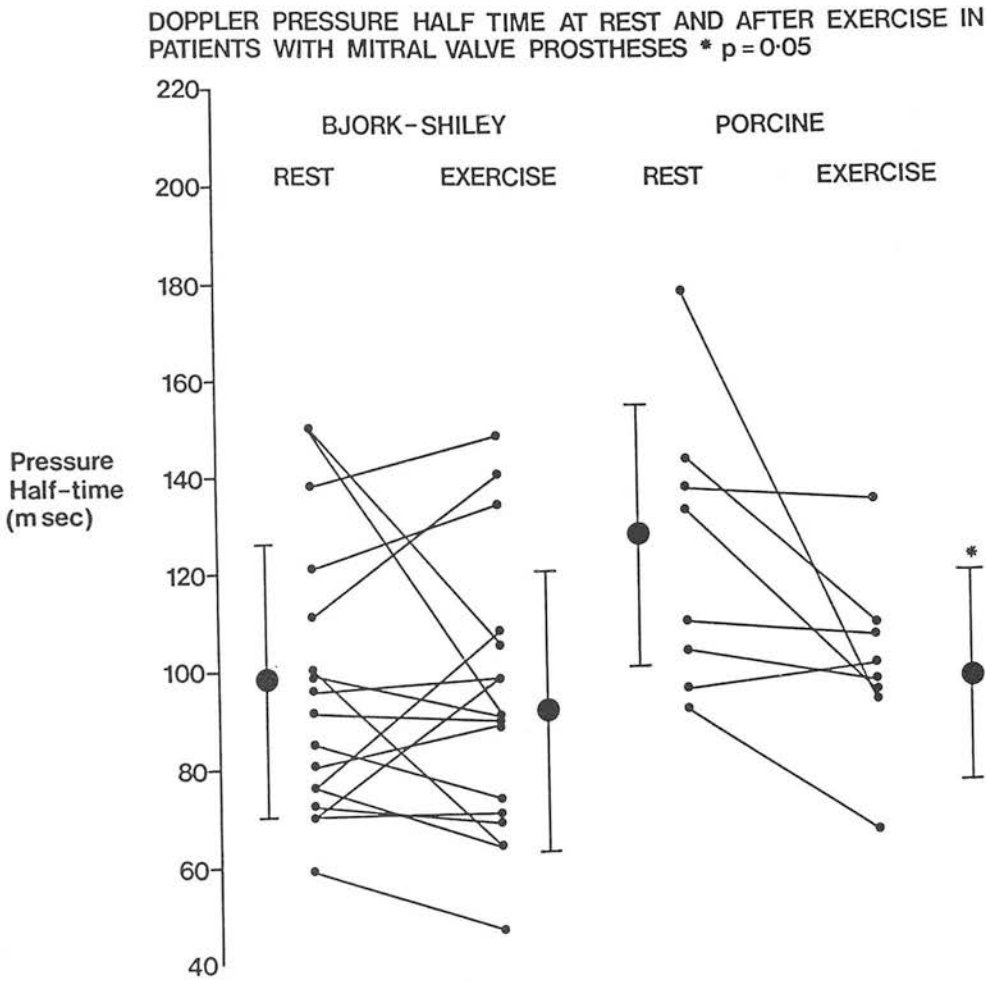
**FIGURE 6.11**

Mean pressure gradient at rest and on exercise for patients with Bjork-Shiley and porcine mitral valve prostheses. Mean values at rest and on exercise are also shown.



**FIGURE 6.12**

Pressure half-time at rest and on exercise for patients with Bjork-Shiley and porcine mitral valve prostheses. Mean values at rest and on exercise are also shown.



## **RESULTS - OBSERVATIONS ON AORTIC VALVE PROSTHESES**

### **Measurement of Left Ventricular Dimensions by M Mode Echocardiography**

M mode echocardiographic recordings suitable for analysis were obtained in 40 of 52 patients with aortic prostheses. The mean left ventricular end diastolic and end systolic dimensions of patients with porcine prostheses were higher than in patients with Bjork-Shiley prostheses (Table 6.3). Mean fractional shortening was similar at 35% in those with porcine prostheses and 38% in those with Bjork-Shiley prostheses (Table 6.3). Three patients with porcine valve prostheses had fractional shortening below 25% (18%, 19% and 23%).

### **Comparison of Mean and Peak Instantaneous Pressure Gradients**

Mean and peak instantaneous pressure gradients were calculated for each patient with one exception where the Doppler signal initially thought to be adequate could not be used for quantitative analysis. Mean pressure gradient correlated closely with peak instantaneous pressure gradient in recordings from patients with porcine and Bjork-Shiley aortic valve replacements. For patients with porcine aortic valve replacements the correlation coefficient between the two measurements was 0.93. The relationship between the two measurements was described by the equation:

Mean pressure gradient (mmHg) =  $0.46 \times$  peak instantaneous pressure gradient + 1.3 mmHg (Fig 6.13).

For patients with Bjork-Shiley aortic valve



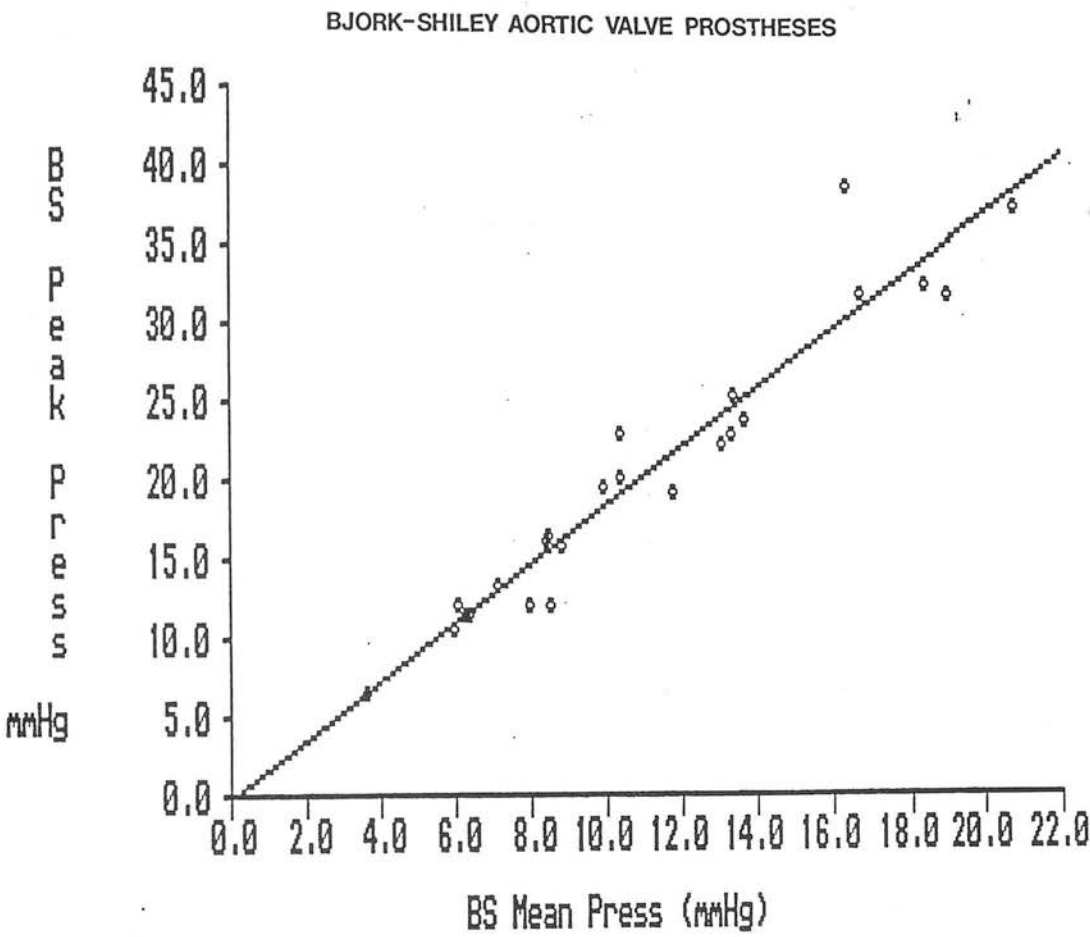
TABLE 6.3

MEAN LEFT VENTRICULAR DIMENSIONS AND FUNCTION IN PATIENTS WITH AORTIC  
VALVE REPLACEMENT

	Bjork-Shiley	Porcine
Left ventricular end diastolic dimension (mm)		
Mean	48	59
SD	6	12
Left ventricular end systolic dimension (mm)		
Mean	29	39
SD	7	14
Fractional shortening (%)		
Mean	38	35
SD	9	12

FIGURE 6.13

Comparison of mean pressure gradient (mean press) and peak instantaneous pressure gradient (peak press) for patients with Bjork-Shiley aortic valve replacements.



replacements the correlation coefficient between the two measurements was 0.96. The relationship between the two measurements was described by the equation:

Mean pressure gradient (mmHg) =  $0.49 \times \text{peak instantaneous pressure gradient} + 0.9 \text{ mmHg}$  (Fig 6.14).

#### **Comparison of Pressure Gradients across Prosthetic Valves of Different Sizes**

There was a wide range of peak instantaneous pressure gradients measured across prosthetic valves of the same size and little difference between valves of different sizes (Figure 6.15). The three patients identified as having impaired ventricular function with fractional shortening of less than 25% had values that were not dissimilar from patients with normal ventricular function (Figure 6.15).

There was also a wide variation in mean pressure gradient across prostheses of different sizes (Fig 6.16).

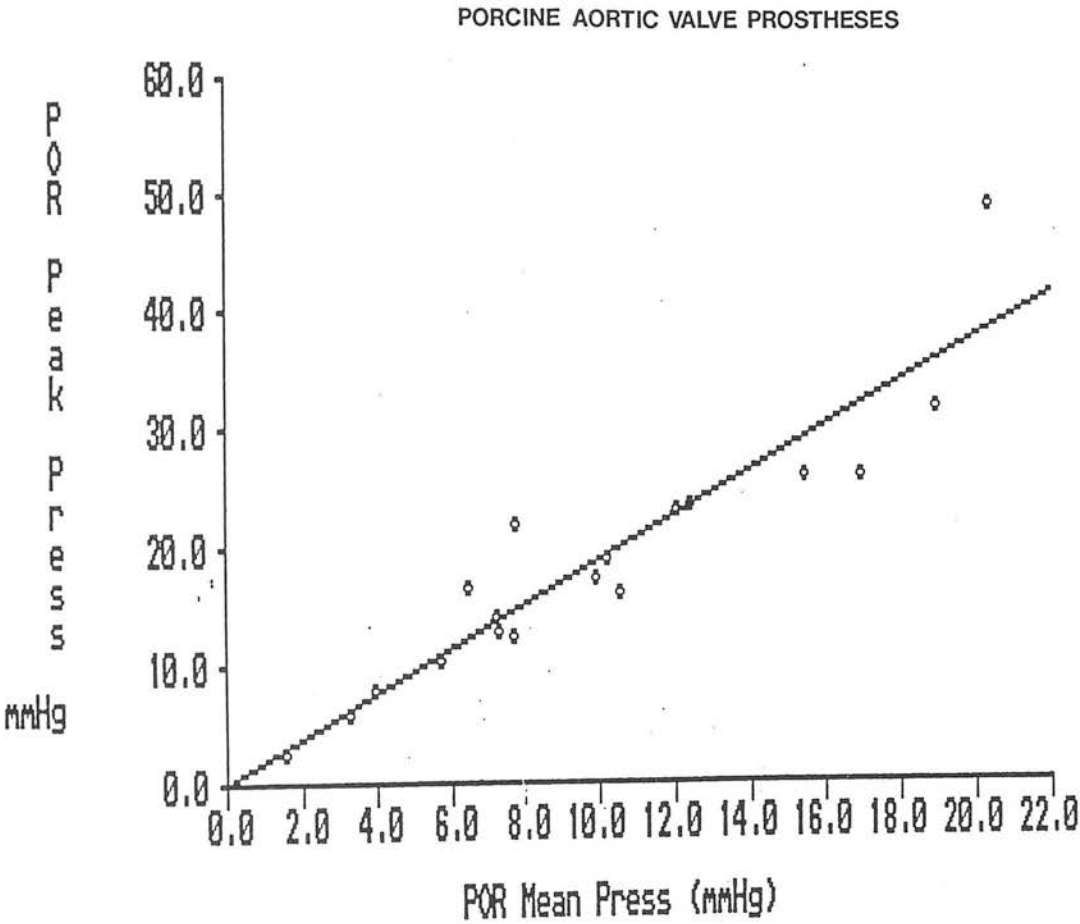
#### **Comparison of Pressure Gradients across Prosthetic Valves of Different Type**

The distribution of sizes of prostheses was similar between patients with Bjork-Shiley and those with porcine prostheses and there was considerable overlap in measured pressure gradients across prostheses of different sizes. Therefore all patients with one type of prosthesis were considered together. The patients with impaired ventricular function were also included, as results based on their inclusion or exclusion did not differ significantly.

The mean of mean pressure gradient across the Bjork-

**FIGURE 6.14**

Comparison of mean pressure gradient (mean press) and peak instantaneous pressure gradient (peak press) for patients with porcine aortic valve replacements.



**FIGURE 6.15**

Peak instantaneous pressure gradients across Bjork-Shiley and porcine aortic valve prostheses of different sizes. Values for patients with impaired ventricular function (fractional shortening < 25%) are indicated by arrows.

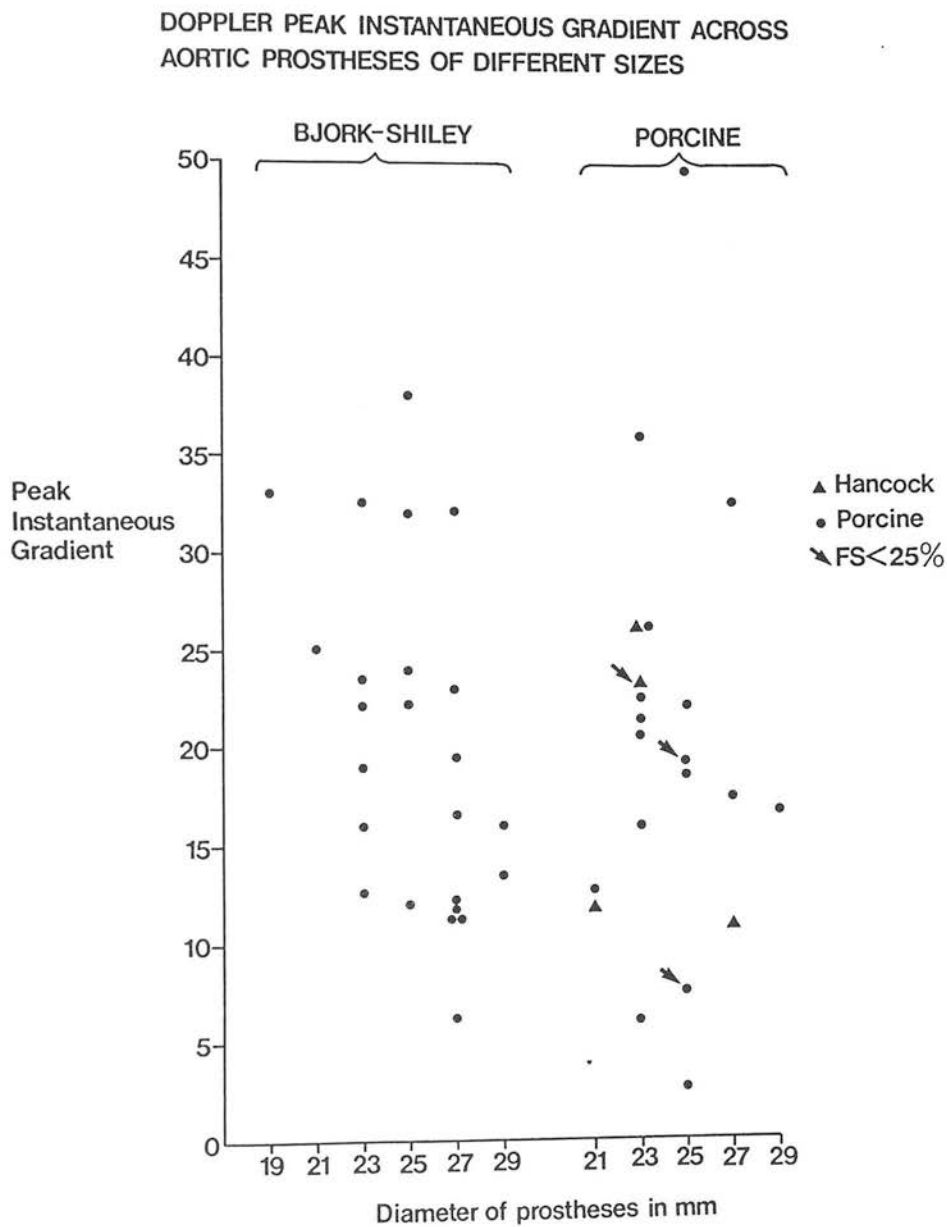
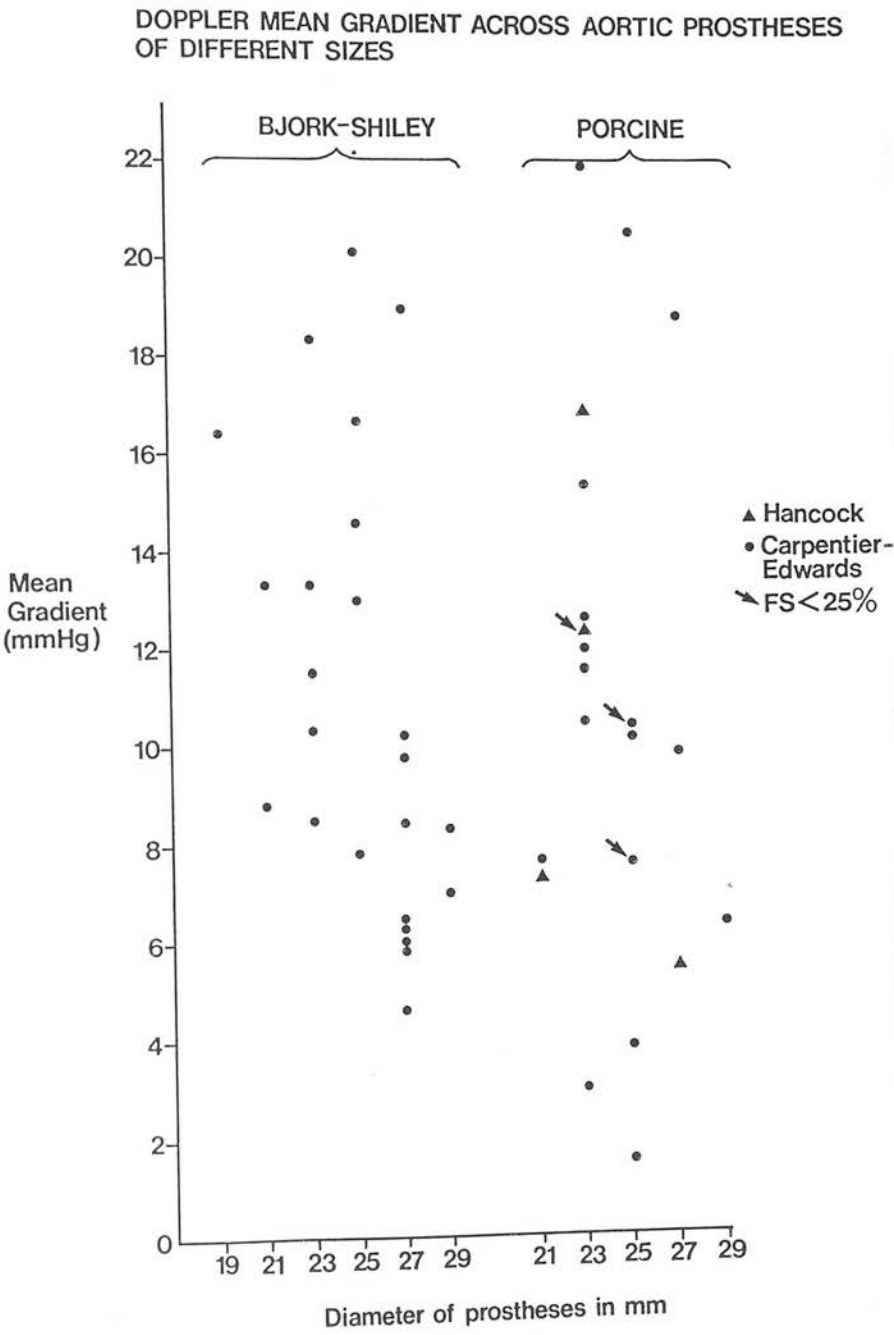


FIGURE 6.16

Mean pressure gradients across Bjork-Shiley and porcine aortic valve prostheses of different sizes. Values for patients with impaired ventricular function (fractional shortening < 25%) are indicated by arrows.



Shiley aortic prostheses was  $11.3 \pm 4.8$  mmHg, and that across the porcine prostheses was  $10.7 \pm 5.5$  mmHg (Figure 6.17). The mean of peak instantaneous pressure gradient across the Bjork-Shiley aortic prostheses was  $20.9 \pm 9.2$  mmHg and that across the porcine prostheses was  $19.9 \pm 10.5$  mmHg (Figure 6.18). There was no significant difference between these values.

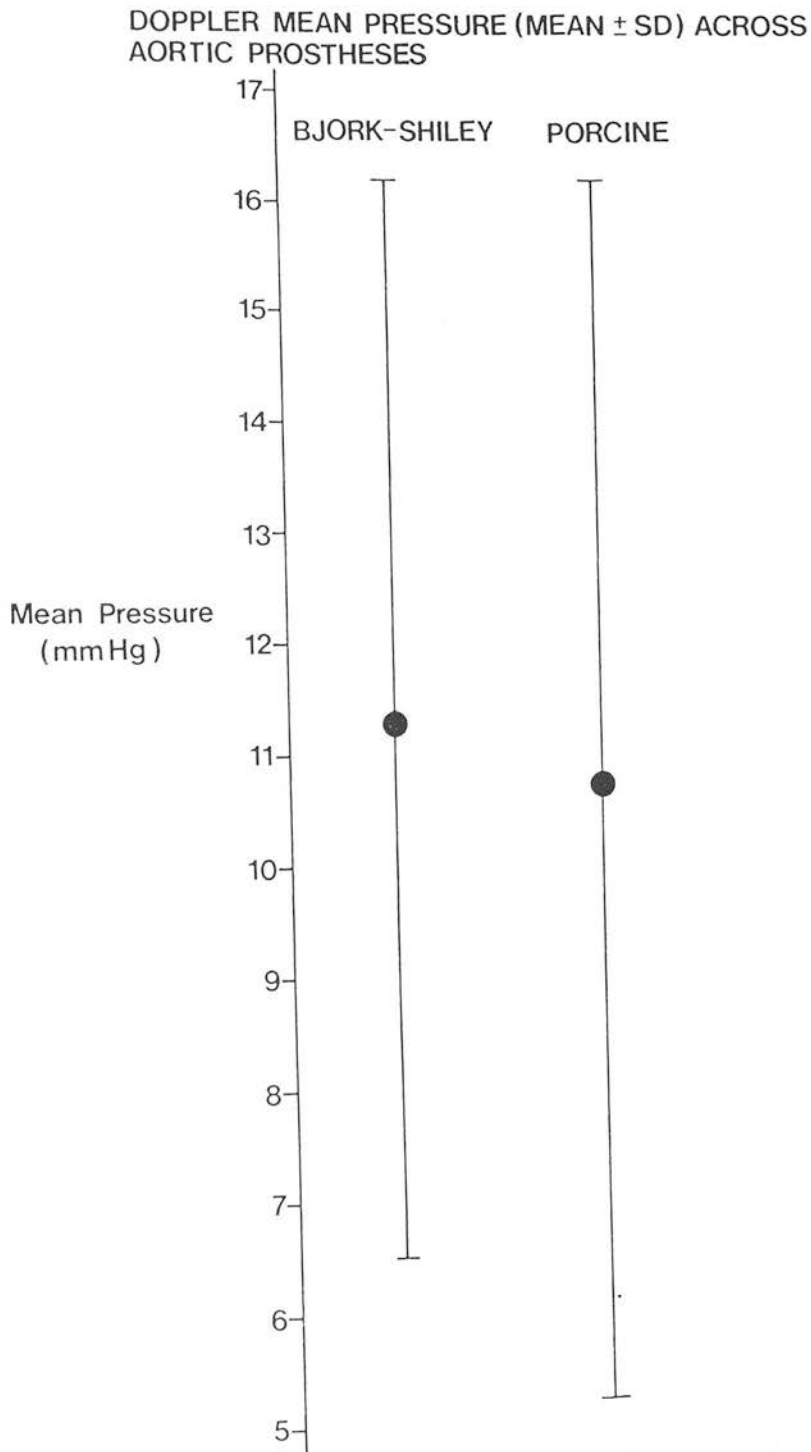
### DISCUSSION

We have shown by means of Doppler echocardiography a small but significant difference in the haemodynamic performance at rest of the Bjork-Shiley 60° tilting disc mechanical prosthesis compared with the Hancock and Carpentier-Edwards porcine prostheses in the mitral position eight to twelve years after implantation. Pressure half-time was shorter in the patients with the Bjork-Shiley prosthesis compared with those with the Hancock and Carpentier-Edwards porcine prostheses. Mean pressure gradient was lower in patients with the Bjork-Shiley prosthesis than those with porcine prostheses in the mitral position, but the difference was not significant.

Mean pressure gradient has consistently been shown to be the Doppler derived measurement which most clearly correlates with data obtained by cardiac catheterisation. Pressure half-time is a reliable index of the degree of native mitral stenosis and has also been shown to correlate with the degree of prosthetic obstruction. Peak instantaneous pressure gradient is not used in the assessment of mitral valve obstruction by cardiac catheterisation. We have shown little correlation between

**FIGURE 6.17**

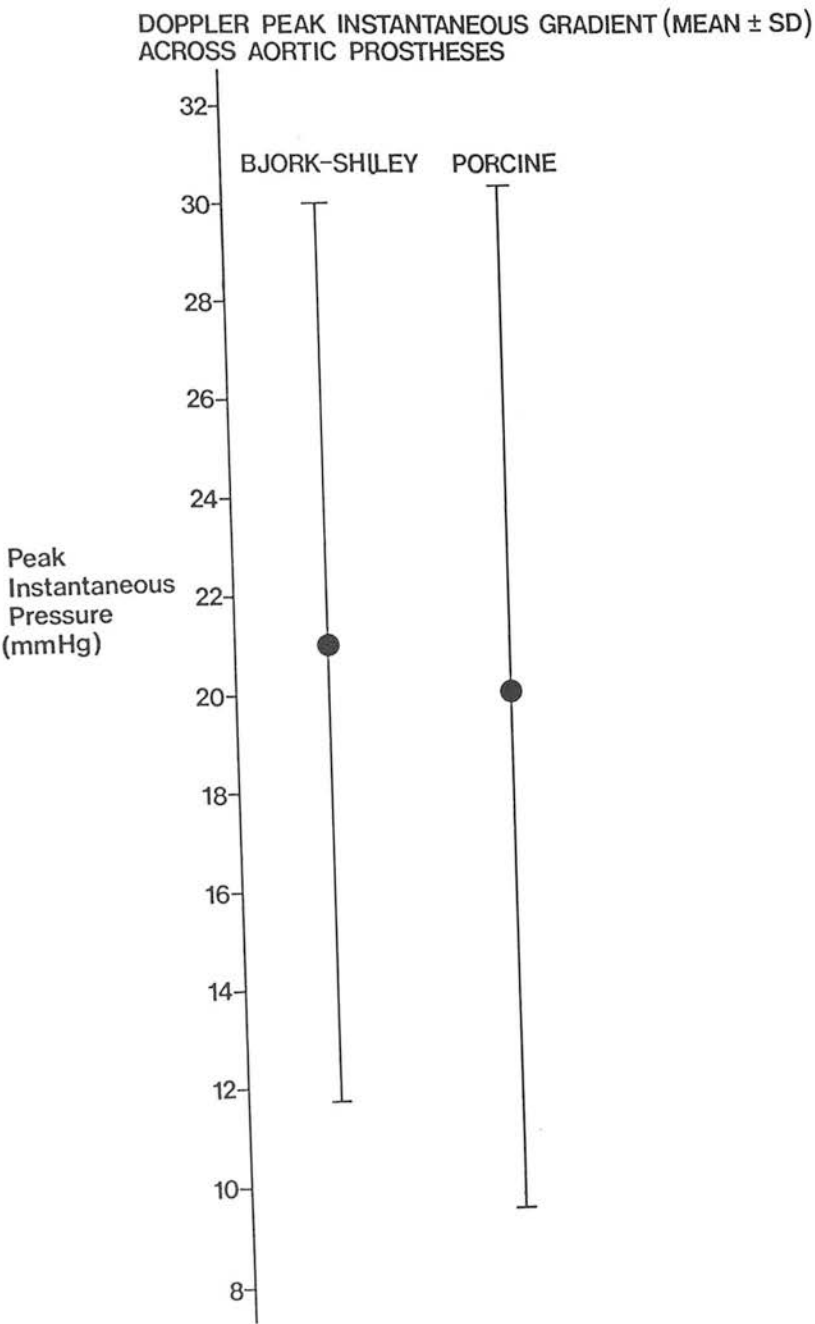
Mean values ( $\pm$ SD) of mean pressure gradient across Bjork-Shiley and porcine aortic valve prostheses.





**FIGURE 6.18**

Mean values ( $\pm$ SD) of peak instantaneous pressure gradient across Bjork-Shiley and porcine aortic valve prostheses.



peak instantaneous pressure gradient and mean pressure gradient and would not consider it a useful measurement of mitral valve obstruction.

When patients with mitral prostheses were exercised there was a similar rise in mean pressure gradient across both the Bjork-Shiley and porcine prostheses. There was no significant change with exercise in the mean of pressure half-time in patients with the Bjork-Shiley prosthesis, but there was a significant fall in pressure half-time in those with porcine prostheses. This change in the Doppler characteristics of the porcine prostheses with exercise suggests that there could be an increase in the effective orifice area of these prostheses with the increased flow across them that occurs with exercise. The difference in pressure half-times noted at rest with both types of prostheses probably does not therefore reflect an important difference in haemodynamic performance between these types of prostheses when used in the mitral position.

We have observed no significant difference in haemodynamic performance between the Bjork-Shiley and Hancock or Carpentier-Edwards porcine prostheses 8-12 years after implantation when used in the aortic position. Mean pressure gradient was similar for both groups of patients with Bjork-Shiley and porcine aortic valve prostheses. Peak instantaneous pressure gradient was also similar for both groups. Peak instantaneous pressure correlated well with mean pressure for patients with both Bjork-Shiley and porcine aortic valve prostheses.

## Limitations of the Study

The most obvious limitations of this study are those of selection bias and sample size. Almost twice as many patients with Bjork-Shiley mitral valve prostheses were studied compared with patients with porcine prostheses. Most patients agreed to come to the hospital for a special visit but it is possible that some patients who did not wish to travel for an extra visit were deterred from doing so by limiting symptoms; this could have been related to dysfunction of their valve prosthesis. Most patients were contacted by letter or telephone following their reply to the questionnaire described in Chapter 4 and only a few refused to come because of limitation of activities, the principle reason given for absence was the need to travel some distance for an extra visit.

Reoperation for prosthetic failure has been required by a larger number of patients with porcine mitral valve prostheses and this has reduced the number of potential patients with porcine mitral prostheses available for study. Only 33 patients in the Edinburgh valve trial who underwent single mitral valve replacement with a porcine prosthesis remain alive with the original prosthesis intact, and sixteen of these were included in the study using Doppler echocardiography. In total of the 241 late survivors of the original valve study 95 underwent a Doppler examination.

In the VA study haemodynamic assessment was carried out 6 months after valve replacement in 248 of 575 patients enrolled in the study with examinations being carried out

in 13 different medical centres and supported by the considerable resources of the Veterans Administration. Our research would have been stronger if it had been possible to include all 241 survivors (or the majority thereof) in the examination by Doppler echocardiography, but limited availability of Doppler equipment and the distribution of the patients over a large geographical area restricted the number of patients that could/would attend for the examination. The conclusions to be drawn from this study are also limited because Doppler examinations were not carried out immediately after the original surgery as well as at 8-12 years after implantation. If this information had been available any observed changes in Doppler indices would have been informative and might have been attributed to changes over time of the performance of the prostheses.

Because of these limitations the conclusion to be drawn from the observed differences at rest in pressure half-time in the Bjork-Shiley and porcine mitral prostheses must be limited; the differences could be due to a deterioration in porcine valve function over time. The greater fall in pressure half-time that occurred with exercise in patients with porcine mitral prostheses compared with Bjork-Shiley mitral prostheses suggests however that there is no significant difference in haemodynamic performance between these two types of prosthesis. The difference in pressure half-time between these types of prosthesis at rest may be due to an initial difference in the Doppler echocardiographic characteristics. For this reason it was interesting to

make a comparison of the results of Doppler echocardiographic examination of these types of prostheses in other studies.

### **Comparisons with Other Studies**

#### **Mitral Prostheses**

Almost all previous assessments of prosthetic valves by Doppler echocardiography have used peak instantaneous pressure (or maximum velocity) and pressure half-time for mitral prostheses. Wilkins et al (1986) calculated mean pressure across tricuspid and mitral prostheses suspected of being obstructive. This was in a small series of 12 patients with mitral and tricuspid prostheses in whom they performed simultaneous catheter and Doppler measurements of mean gradient finding the two methods produced results in close agreement.

Peak velocity or peak instantaneous pressure across the mitral valve would be expected to vary with different loading conditions affecting left atrial pressure, and indeed we have shown a poor correlation between peak instantaneous pressure and mean gradient. The values of peak velocity recorded across mitral prostheses in our study showed a wide variation in patients with both porcine and Bjork-Shiley prostheses. The values obtained did not differ from those reported in other series (Tables 6.4 and 6.5). Similarly there was a wide variation in pressure half-time in patients in our study and in those reported by others. Pressure half-time was similar for patients in our study and in other studies. Greater pressure half-times have been reported in other studies for porcine mitral

TABLE 6.4

COMPARISON WITH OTHER STUDIES: MITRAL PORCINE PROSTHESES

REFERENCE	VALVE	AGE (yrs)	SIZE (mm)	NO PATIENTS	PEAK VELOCITY cm/s (SD)	MEAN GRADIENT mmHg (SD)	PRESSURE HALF-TIME msec (SD)
Williams and Labovitz (1985)	H CE	NA	28 31	16	-	15 (-)	105 (26)
Sagar et al (1986)	H	0-7 (mean 2.8)	27	3	158 (29)	5 (2)	169 (64)
			29	9	133 (25)	2 (0.7)	146 (17)
			31	8	100 (10)	2 (0.9)	138 (16)
			33	3	87 (25)	2 (2)	116 (11)
Gibbs et al (1986)	CE	0-8	27 )				
			29 )	38	164 (24)	-	90 (23)
			31 )				
Ryan et al (1986)	H	0-8	23-)	29	136 (24)	-	136 (18)
	CE	(mean 4)	35 )				
This study	H	8-12	31 )	16	149 (25)	3.4 (1.4)	114 (36)
	CE	(mean 9.8)	33 )				
			35 )				

TABLE 6.5

COMPARISON WITH OTHER STUDIES: MITRAL BJORK-SHILEY PROSTHESES

REFERENCE	AGE (yrs)	SIZE (mm)	NO PATIENTS	PEAK VELOCITY cm/s (SD)	MEAN GRADIENT mmHg (SD)	PRESSURE HALF-TIME msec (SD)
Williams and Labovitz (1985)	NA	27 ) 29 ) 31 )	35	-	10 (-)	88 (21)
Sagar et al (1986)	0-7 (mean 2.8)	29 31	7 10	133 (31) 123 (27)	2 (0.8) 2 (1.9)	107 (7) 100 (12)
Gibbs et al (1986)	NA	23 - 31	- 31	- 147 (30)	-	77 (18)
Panidis et al (1986)	NA	-	8	160 (30)	5 (2)	100 (15)
This study	8-12 (mean 10.3)	31 33	34	151 (20)	3.1 (1.1)	90 (28)

prostheses than for Bjork-Shiley prostheses (Tables 6.4 and 6.5). Most patients studied in other series had prostheses which had been implanted only a few years previously and none more than eight years previously. Gibbs et al (1986) noted a non-significant trend towards an increase in pressure half-time increasing with time since implantation of the Carpentier-Edwards mitral prosthesis. Ryan (personal communication) noted a mean pressure half-time of 124 msec for valves implanted less than 4 years previously, and 148 msec for those implanted more than 4 years previously. The similarity of the results of our study compared with the results of other series do not however suggest that there is a significant deterioration in haemodynamic performance of porcine prostheses over this period of time. The consistently greater pressure half-time, albeit small, observed with porcine mitral prostheses suggests rather that this is an inherent Doppler echocardiographic characteristic of these prostheses when used in the mitral position. The fall in pressure half-time with exercise that occurred in patients with porcine mitral prostheses also suggests that the differences observed at rest do not represent an important haemodynamic advantage for the Bjork-Shiley prosthesis.

#### Aortic prostheses

We have shown that haemodynamic performance of the Bjork-Shiley, Hancock and Carpentier-Edwards prostheses is similar in the aortic position 8 - 12 years after implantation.

The results of measurements of peak instantaneous



pressure gradient in our study are similar to those reported by others in patients with prostheses implanted for lesser periods of time (Tables 6.6, 6.7). Peak instantaneous pressure gradient was indeed lower than in some other studies and there is therefore no suggestion of deterioration of haemodynamic performance with increasing age of the prosthesis. Mean gradient has not been reported in other studies and comparison is not possible.

### **Conclusions**

We can only conclude that within the restrictions of our study, measurements using Doppler non-invasive techniques indicate no quantifiable deterioration or difference in the haemodynamic performance of Bjork-Shiley or porcine prostheses used in the mitral or aortic positions for periods extending 8 to 12 years after implantation. There are severe limitations in data available and we would suggest that Doppler measurements be included in the examination of selected patients receiving replacement valves soon after their operation; this early data would provide a useful baseline for comparison with subsequent non-invasive measurements taken as the valves age in use.

TABLE 6.6

## COMPARISON WITH OTHER STUDIES: AORTIC PORCINE PROSTHESES

REFERENCE	VALVE	YEARS FROM IMPLANTATION	SIZE (mm)	NO PATIENTS	PEAK INSTANTANEOUS GRADIENT	MEAN GRADIENT
Williams and	H	NA	23 )			
Labovitz (1985)	CE		25 )	27	23 (10)	-
			27 )			
			29 )			
Sagar et al	H	0-7	23	7	18 (4)	-
(1986)		(mean 2.8)	25	10	16 (2)	-
			27	5	15 (3)	-
Gibbs et al	CE	0-8	21 )			
(1986)			23 )			
			25 )	24	24 (10)	-
			27 )			
			29 )			
This study	H	8-12	21 - )	22	18 (11)	10 (5)
	CE	(mean 10.1)	29 )			

TABLE 6.7

## COMPARISON WITH OTHER STUDIES: AORTIC BJORK-SHILEY PROSTHESES

REFERENCE	AGE (yrs)	SIZE (mm)	NO PATIENTS	PEAK INSTANTANEOUS GRADIENT mmHg (SD)	MEAN GRADIENT mmHg (SD)
Williams and Labovitz (1985)	NA	21 ) 23 ) 25 ) 27 ) 29 )	33	22 (10)	-
Sagar et al (1986)	0-7 (mean 2.8)	23 25 27	6 9 5	33 (4) 19 (5) 16 (5)	- - -
Panidis et al (1986)	NA	19 21 23 25	4 6 14 9	38 (20) 26 (7) 21 (12) 20 (9)	- - - -
This study	8-12 (mean 10.2)	21 -) 29 )	25	20 (9)	11 (5)

## CHAPTER 7

### **SUMMARY AND CONCLUSIONS**

From 1975 to 1979 in Edinburgh Royal Infirmary 540 patients were entered into a randomised trial and received either a mechanical (Bjork-Shiley) or porcine heterograft (Hancock or Carpentier-Edwards) prosthesis. The principle advantage of the porcine heterograft prosthesis is that patients do not necessarily require to take anticoagulant treatment. After a mean period of 5 years of follow-up no significant advantage to any of these three prostheses had been observed.

In 1977 the Veterans Administrations (VA) in the United States started a similar randomised trial comparing the Bjork-Shiley with the Hancock prosthesis. After a mean period of 5 years of follow-up there was also no significant difference in patient survival but there was a significantly increased occurrence of clinical complications related to the valve prosthesis in those receiving a Bjork-Shiley prosthesis. These complications were related to a greater incidence of bleeding in patients with this prosthesis necessitating long-term treatment with anticoagulants; this finding was at variance with the results of the Edinburgh study in which bleeding occurred much less frequently. The difference in results was attributed to differences in the methods of control of anticoagulant treatment in Edinburgh, and in the United States, and also to differences in the populations studied.

The work has been extended in Edinburgh and after a mean follow-up period of 10.5 years we have observed no

difference in survival between those receiving a mechanical or a porcine prosthesis. Reoperation for valve failure, however, was necessary in significantly more patients with a porcine prosthesis than in those receiving a Bjork-Shiley prosthesis. Seventeen patients with the Bjork-Shiley, and 53 with a porcine prosthesis (20 with Hancock, and 33 with Carpentier-Edwards) have required reoperation to replace the randomised prosthetic valve. This difference was almost exclusively due to cusp failure of porcine prostheses occurring more than 5 years after implantation.

Degeneration of porcine prostheses might be gradual, and failure of a mechanical prosthesis might be abrupt and catastrophic, and we thought it possible that the number of patients undergoing reoperation for failure of a porcine prosthesis might possibly have been offset by a similar number of patients with Bjork-Shiley prostheses dying suddenly due to prosthetic failure. We therefore examined actuarial survival with reoperation or cardiac death as an end point. Actuarial survival-free from reoperation or cardiac death was significantly higher in those receiving a Bjork-Shiley prosthesis than in those receiving a porcine prosthesis when all patients and those receiving a mitral valve replacement were considered, but not when those receiving an aortic valve replacement were considered.

Bleeding occurred on 34 occasions in 28 patients with the Bjork-Shiley, and on 18 occasions in 15 patients with porcine prostheses. Death and valve related events (reoperation, bleeding and complications of anticoagulation, systemic embolism and bacterial

endocarditis) were considered as end-points for actuarial analysis. There was a non significant trend towards improved actuarial "event-free" survival for those patients receiving the Bjork-Shiley prosthesis when all patients, and those receiving a mitral valve replacement were considered, but not when those receiving aortic valve replacement were considered. The differences demonstrated between prostheses in the Edinburgh trial have only become apparent after ten years, and this emphasises the importance of such a period of observation in the evaluation of heart valve prostheses.

Doppler ultrasound techniques have been used to compare the haemodynamic performance of the Bjork-Shiley and porcine prostheses, an average of 10 years after implantation, in 102 patients enrolled in the Edinburgh Trial. No significant difference in peak instantaneous pressure gradient, or mean pressure gradient across the prosthesis was observed in patients who had undergone either aortic valve replacement, or mitral valve replacement.

Pressure half-time is a Doppler-derived index of obstruction used to evaluate stenotic mitral valves. We found a significantly lower pressure half-time in patients with the Bjork-Shiley mitral valve prosthesis compared with patients with porcine mitral valve prostheses. Some of these patients underwent exercise testing, and pressure half-time was observed to fall with exercise in those with porcine prostheses, but remained unchanged in those with Bjork-Shiley prostheses. This suggests that the

differences in pressure half-time observed at rest do not represent an important haemodynamic advantage for the Bjork-Shiley prosthesis.

We compared the results obtained in this study with those reported in other series of Doppler echocardiographic evaluations of Bjork-Shiley and porcine prostheses. We conclude from our measurements and from this comparison that there is no quantifiable deterioration or difference in the haemodynamic performance of Bjork-Shiley or porcine prostheses used in the mitral or aortic positions for periods extending 8 - 12 years after implantation. There are limitations in the data available and we would suggest that in future Doppler measurements might be included in the examination of selected patients receiving replacement valves soon after their operation and that this early data would provide useful baseline information for comparison with subsequent non-invasive measurements taken as the valves age in use.

In the light of these results what recommendation for the selection of type of prosthesis for patients undergoing valve replacement can be made? Our results suggest that patients who because of atrial fibrillation, or for other reasons would normally continue anticoagulants after valve replacement should receive a mechanical prosthesis. In our practice this would include the majority of patients undergoing replacement of the mitral valve. Indeed, with the increased risk of reoperation more than 5 years after implantation of the prosthesis it would appear that patients undergoing mitral valve replacement should

receive a mechanical prosthesis unless there is a clear contra-indication to anticoagulants. There is no apparent clear advantage for the use of a mechanical prosthesis in those undergoing aortic valve replacement, but younger patients could benefit from a mechanical prosthesis of proven durability.

It is important that anticoagulant control should not lead to an increased risk of bleeding, and warfarin control at a prothrombin ratio of 2.0 - 4.0 in the United Kingdom, which is equivalent to a ratio of 1.3 - 2.0 in the U.S.A., would appear to give a satisfactory reduction in the risk of embolism, without excessive risk of bleeding.

Porcine bioprosthetic valves will continue to be useful for patients in whom anticoagulants must be avoided, but this selection should be made in the knowledge that with these prostheses there is a greater probability that a second operation could be required due to valve deterioration at a later date.



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